Uniform Medical Plan coverage limits

Updates effective 7/1/2025

The benefit coverage limits listed below apply to these UMP plans:

- Uniform Medical Plan (UMP) Classic (PEBB)
- UMP Select (PEBB)
- UMP Consumer-Directed Health Plan (UMP CDHP) (PEBB)
- UMP Plus–Puget Sound High Value Network (UMP Plus–PSHVN) (PEBB)
- UMP Plus–UW Medicine Accountable Care Network (UMP Plus–UW Medicine ACN) (PEBB)

- UMP Achieve 1 (SEBB)
- UMP Achieve 2 (SEBB)
- UMP High Deductible Plan (SEBB)
- UMP Plus–Puget Sound High Value Network (UMP Plus–PSHVN) (SEBB)
- UMP Plus–UW Medicine Accountable Care Network (UMP Plus–UW Medicine ACN) (SEBB)

Some services listed under these benefits have coverage limits. These limits are either determined by a Health Technology Clinical Committee (HTCC) decision or a Regence BlueShield medical policy. **The table below does not include every limit or exclusion under this benefit. For more details, refer to your plan's Certificate of Coverage.**

Uniform Medical Plan Pre-authorization List

The Uniform Medical Plan (UMP) Pre-authorization List includes services and supplies that require pre-authorization or notification for UMP members.

NOTE: This document includes links to external webpages and documentation. To search inside this document, use CTRL+F for PCs or Command+F for Macs, and type in your search term.

Pharmacy

UMP has a separate vendor – Washington State Rx Services – for the prescription drug benefit. Pre-authorization is necessary for certain injectable drugs that are not normally approved for self-administration when obtained through a retail pharmacy or a network mail-order pharmacy. These drugs are indicated on the UMP Preferred Drug List.

Drugs usually payable under the member's medical benefit will continue with the same Regence process. The Medical Policies associated with these medications are attached to this document. These Medical Policies can also be found by going to https://regence.myprime.com/en/forms/coverage-determination/prior-authorization.html and searching for the specific medication by utilizing CTRL+F.

Medications in blue = HTCC decision followed for UMP members, found at: https://www.hca.wa.gov/assets/program/HA-PRP-final-findings-decision.pdf

Medications in green = HTCC decision followed for UMP members when the diagnosis is chronic migraine as of 01/01/18, found at: https://www.hca.wa.gov/assets/program/chronic-migraine-final-findings-decision-revised-20220520.pdf

Medications in orange do not yet have policies created, but still require prior authorization = Falls under the New to Market policy dru517

Infusion Drug Site of Care

Certain provider administered infusion medications covered on the medical benefit are subject to the Site of Care Program (dru408) medication policy. This policy does not apply to members covered under UMP Plus plans.

Active Medical Drug Prior Authorization List

Abecma
Abraxane
Actemra
Adakveo
Adbry
Adcetris
Adstiladrin
Adynovate
Adzynma
Afstyla
Ahzantive
Ajovy
Aldurazyme
Alhemo
Alprolix
Altuviiio
Alyglo
Alymsys
Amondys 45
Amtagvi
Amvuttra
Anktiva
Aralast NP
Aucatzyl
Avastin
Aveed
Avsola
Avtozma
Avzivi
Azedra
Azmiro
Bavencio
Beleodaq
Beovu
Beqvez
Berinert
Besponsa
Bizengri
Bkemv
Blincyto
Bomyntra
Botox
Breyanzi
Brineura
Briumvi
Byooviz
Cablivi
Casgevy
Cerezyme
Cimzia
Cinqair
Cinryze
Columvi
Compounded Medications
Conexxence
Cosela
Cosentyx
Crysvita
Cutaquig
Cuvitru
Cyramza
Darzalex
Darzalex Faspro
Datroway
Daxxify
Denosumab-bnht
Denosumab-dssb
Durolane
Dysport
Elahere
Elaprase
Elelyso
Elevidys
Eloctate
Elrexfio
Elzonris
Empliciti
Encelto
Enhertu
Enjaymo
Entyvio
Enzeevu
Epkinly
Epysqli
Esperoct
Euflexxa
Evenity
Evkeeza
Exondys
Eylea
Eylea HD
Fabrazyme
Fasenra
Folotyn
Fyarro
Fylnetra
Gamifant
Gazyva
Gel-One
Gel-Syn 3
GenVisc 850
Givlaari
Glassia
Hemgenix
Hemlibra
Herceptin
Herceptin
Hylecta
Hercessi
Herzuma
Hyalgan
Hymovis
Hympavzi
Idelvion
Ilaris
Ilumya
Imaavy
Imdelltra
Imfinzi
Imlygic
Imuldosa
Inflectra
Istodax
IVIG/SCIG[1]
Ixifi
Izervay
Jelmyto
Jemperli
Jivi
Jobevne
Jubbonti
Kadcyla
Kalbitor
Kanuma
Kebilidi
Keytruda
Kimmtrak
Kisunla
Kybella
Kymriah
Kyprolis
Lamzede
Lanreotide Injection
Lemtrada
Lenmeldy
Leqembi
Leqvio
Letybo
Libtayo
Loqtorzi
Lucentis
Lumizyme
Lunsumio
Lutathera
Luxturna
Lyfgenia
Lymphir
Margenza
Mepsevii
Monjuvi
Monovisc
Mylotarg
Myobloc
Naglazyme
Neulasta/Onpro
Neupogen
Nexviazyme
Niktimvo
Nivestym
Nplate
Nucala
Nulibry
Nypozi
Ocrevus
Ocrevus Zunovo
Ogivri
Omvoh
Onivyde
Onpattro
Ontruzant
Opdivo
Opdivo Qvantig
Opdualag
Opfolda
Opuviz
Orencia
Orthovisc
Osenvelt
Ospomyv
Otulfi
Oxlumo
Padcev
Palforzia
Palynziq
Pavblu
Pedmark
Penpulimab-kcqx
Perjeta
Phesgo
Piasky
Pluvicto
Polivy
Pombiliti
Prolaryn
Prolastin-C
Prolia
Provenge
Pyzchiva
Qalsody
Qfitlia
Radicava
Radiesse
Rebinyn
Reblozyl
Rebyota
Releuko
Remicade
Renflexis
Revcovi
Riabni
Rituxan Hycela
Rituxan IV
Rivfloza
Roctavian
Rolvedon
romidepsin
Ruconest
Rybrevant
Ryoncil
Ryplazim

[1] Includes Asceniv, Bivigam, Carimune, Flebogamma, Gammagard S/D, Gammagard, Gammaplex, Gamunex-C, Gammaked, Hizentra, HyQvia, Octagam, Panzyga, Privigen, Xembify

Active Medical Drug Prior Authorization List

Rystiggo
Rytelo
Ryzneuta
Sandostatin LAR
Saphnelo
Sarclisa
Scenesse
Sculptra
Selarsdi
Signifor LAR
Simponi Aria
Site of Care
Skyrizi
Skysona
Soliris
Somatuline
Depot
Somavert
Spevigo
Spinraza
Spravato
Stelara (IV
infusion)
Steqeyma
Stimufend
Stoboclo
Supartz
Supprelin LA
Susvimo
Syfovre
Synagis
SynoJoynt
Synvisc
Synvisc-One
Talvey
Tecartus
Tecelra
Tecentriq
Tecvayli
Tepezza
Testopel
Tevimbra
Tezspire
Tivdak
Tofidence
TriLURON
TriVisc
Trodelvy
Tyenne
Tyruko
Tysabri
Tzield
Udencya
Ultomiris
Unloxcyt
Uplizna
Uptravi injection
Ustekinumab-
stba
Vabysmo
Veopoz
Viltepso
Vimizim
Visco-3
VPRIV
Vyepti
Vyloy
Vyondys 53
(golodirsen)
Vyvgart
Vyxeos
Wezlana
Wyost
Xbryk
Xenpozyme
Xeomin
Xgeva
Xipere
Xolair
Ycanth
Yervoy
Yesafili
Yescarta
Yesintek
Yondelis
Zaltrap
Zemaira
Zepzelca
Ziihera
Zilretta
Zolgensma
Zylonta
Zynteglo
Zynyz

[1] Includes Asceniv, Bivigam, Carimune, Flebogamma, Gammagard S/D, Gammagard, Gammaplex, Gamunex-C, Gammaked, Hizentra, HyQvia, Octagam, Panzyga, Privigen, Xembify

Regence Oregon and Utah | Regence Idaho and select counties of Washington

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Medication Policy Manual

Policy No: dru006

Topic: Botulinum toxin type A injection:

- Botox, onabotulinumtoxinA
- Dysport, abobotulinumtoxinA
- Xeomin, incobotulinumtoxinA
- Daxxify, daxibotulinumtoxinA

Date of Origin: January 1996

Committee Approval Date: December 7, 2023

Next Review Date: 2024

Effective Date: January 15, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Botulinum toxin is a neurotoxin that is injected into a muscle to cause temporary paralysis or relaxation of that muscle. There are four commercial botulinum toxin type A products available: Botox (onabotulinumtoxinA), Dysport (abobotulinumtoxinA),Xeomin (incobotulinumtoxinA), and Daxxify (daxibotulinumtoxinA). Botulinum toxin type B (rimabotulinum, Myobloc) is covered in a separate policy.

Please note: Botulinum toxin for use in gender affirming care is covered in a separate policy, Gender-Affirming Care Products, dru757

Policy/Criteria

Most contracts require pre-authorization approval of botulinum toxin type A prior to coverage.

I. Continuation of therapy (COT): Botulinum toxin type A (Botox, Dysport, Xeomin, Daxxify) may be considered medically necessary for COT when criterion A, B, or C below are met.

A. For potentially cosmetic indications, including **hyperhidrosis**, full policy criteria below must be met for coverage.

OR

B. For all other indications, criteria 1 and 2 below must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Botulinum toxin type A (Botox, Dysport, Xeomin, Daxxify) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criterion A or B below are met:

A. **Dystonia or Spastic conditions**, due to one of the following diagnoses:

1. **Cerebral Palsy**

2. **Cervical dystonia with torticollis** with documentation of involuntary contractions of the neck muscles resulting in twisting and repetitive movements, and/or abnormal postures (as documented on physical exam)

3. **Demyelinating diseases of CNS**, including, but not limited to, central demyelinating of corpus callosum, leukodystrophy, multiple sclerosis (MS), neuromyelitis optica (NMO), Schilder's disease

4. **Dysphonia**, including spasmodic dysphonia, laryngeal spasm; laryngeal adductor spastic dysphonia, or stridulus

5. **Facial nerve disorders** (such as blepharospasm, facial/hemifacial spasms, facial nerve VII disorders, facial myokymia, Melkersson syndrome)

6. **Focal upper limb/hand dystonia** (such as Organic writer's cramp)

7. **Lower limb spasticity** (including increased muscle tone in the ankle and toes)

8. **Oromandibular dystonia** (such as orofacial dyskinesia, jaw closure dystonia, Meige syndrome)
9. **Spastic hemiplegia or paraplegia** [including hereditary, related to a stroke (CVA), or related to a spinal cord injury (SCI)]
10. **Thoracic outlet syndrome**, with documentation of functional impairment.
11. **Torticollis, spasmodic or unspecified**, with documentation of involuntary contractions of the neck muscles resulting in twisting and repetitive movements, and/or abnormal postures
12. **Torsion dystonia** [including both symptomatic (acquired) or idiopathic (primary or genetic; a.k.a. Oppenheim's dystonia)]
13. **Upper limb spasticity**

OR

B. **Strabismus**, resulting in vision changes.

III. New starts (treatment-naïve patients): Botulinum toxin A (Botox, Dysport, Xeomin, Daxxify) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) for the diagnoses listed below, that one of the following criterion A through J below is met:

A. **Anal fissures,** when prior treatment with one or more therapeutic alternatives, such as nitroglycerin ointment or diltiazem cream, has been ineffective, not tolerated, or is contraindicated.

OR

B. **Congenital aganglionic megacolon (Hirschsprung disease),** with documented severe refractory constipation due to increased anal sphincter tone **or** withholding and when prior treatment with bowel regimen for constipation has been ineffective, not tolerated, or is contraindicated.

OR

C. **Endoscopically-administered botulinum,** when criteria 1 and 2 below is met:

1. An upper gastrointestinal diagnosis such as (but not limited to) **dysphagia, gastroparesis, or achalasia/cardiospasm (primary)**.

AND

2. Documented symptoms despite use of standard therapies, such as:
   - **a.** Dysphagia: Diet modification (such as smaller meals, softer foods), and/or occupational therapy.
   - **b.** Gastroparesis: Diet modification, promotility medications, such as metoclopramide, cisapride, erythromycin, or removal/reduction of underlying etiology (such as taper of opioids).
   - **c.** Achalasia/cardiospasm (primary): Dilation therapy, unless the patient is considered a poor surgical candidate.

OR

D. **Hyperhidrosis** (including axillary, palmar and gustatory hyperhidrosis), when criteria 1 through 3 below are met:

1. The hyperhidrosis is documented as persistent and severe.

AND

2. The hyperhidrosis has resulted in a significant medical complication* including a through e:

a. Acrocyanosis of the hands.

OR

b. Recurrent skin maceration with secondary bacterial or fungal infection.

OR

c. Recurrent secondary infections.

OR

d. Persistent eczematous dermatitis.

OR

e. Documentation of inability to perform critical activities of daily living or demands of employment due to hyperhidrosis.

AND

3. Treatment with at least one of the following has been ineffective, not tolerated, or all are contraindicated:

a. Prescription antiperspirants [e.g. aluminum chloride hexahydrate 20% (Drysol)].

OR

b. Oral or topical anticholinergics (e.g. glycopyrrolate or oxybutynin).

***PLEASE NOTE:** Medical treatment of persistent hyperhidrosis is considered not medically necessary in the absence of significant medical complications associated with the condition. Skin irritation, skin maceration without secondary infection, need for frequent changing of clothing, or psychosocial distress alone are not considered to be significant medical complications.

OR

E. **Migraine headache, chronic and severe,** when criteria 1 through 3 below are met:

1. A neurologist or headache specialist has thoroughly evaluated the member and has established and documented a diagnosis of chronic migraine headaches.

AND

2. Documentation of baseline headache days per month, including the number of migraines based on a headache diary OR chart notes, documenting migraine frequency, severity and characteristics.

AND

3. Documentation of an adequate trial of at least ONE prophylactic therapy, as specified in criteria a through d below were either ineffective, not tolerated, or ALL are contraindicated:

a. Topiramate **OR** divalproex sodium (Depakote).

OR

b. A beta blocker (such as propranolol, metoprolol, or atenolol).

OR

c. Venlafaxine OR a tricyclic antidepressant (such as amitriptyline or nortriptyline).

OR

d. Calcitonin gene-related peptide (CGRP) monoclonal antibody or oral CGRP antagonists [such as Aimovig (erenumab), Emgality (galcanezumab), Vyepti (eptinezumab), or Ajovy (fremanezumab), Nurtec (rimegepant), Qulipta (atogepant)] when used for prophylaxis.

PLEASE NOTE: CGRPs used for acute abortive therapy [such as "as needed" rimegepant (Nurtec ODT) or Ubrelvy (ubrogepant)] are not included in this criterion.

OR

F. **Pelvic floor dysfunction** (such as due to levator spasm, pelvic floor spasm), when criteria 1 and 2 below are met:

1. Documented pain and/or functional impairment associated with the pelvic floor dysfunction, such as pelvic pain, vaginismus, and/or dyspareunia.

AND

2. Prior treatment with another treatment option for pelvic floor dysfunction (such as physical therapy, muscle relaxants, trigger point injections, surgery) has been ineffective, not tolerated, or is contraindicated.

OR

G. **Raynaud's syndrome or systemic sclerosis-associated digital ulcers,** when criteria 1 and 2 below is met:

1. Documented pain and/or functional impairment associated with the vasospasm and/or digital ulcers.

AND

2. Prior treatment with a dihydropyridine calcium channel blocker (such as amlodipine, nifedipine) or another vasodilator (such as topical nitroglycerin, a phosphodiesterase type 5 inhibitor, or an angiotensin II receptor blocker) has been ineffective, not tolerated, or is contraindicated.

OR

H. **Sialorrhea** (drooling).

OR

I. **Urinary incontinence,** due to detrusor overactivity [idiopathic or neurogenic (e.g. due to spinal cord injury, multiple sclerosis) or overactive bladder (OAB)], when therapy with anticholinergic agents **or** Myrbetriq (mirabegron) is ineffective or not tolerated.

OR

J. **Refractory postherpetic neuralgia (PHN)** when criteria 1 and 2 below are met:

1. Documented pain and/or functional impairment associated with postherpetic neuralgia, such as a burning, sharp, or stabbing pain that is constant or intermittent.

AND

2. Documentation that adequate trials of BOTH of the following (criteria a and b below) were either ineffective, not tolerated, or are contraindicated.

a. A gabapentinoid [such as gabapentin or pregabalin (Lyrica)].

AND

b. A tricyclic antidepressant (TCA, such as amitriptyline or nortriptyline) OR a serotonin-norepinephrine reuptake inhibitor (SNRI, such as duloxetine or venlafaxine).

IV. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers botulinum toxin type A (Botox, Dysport, Xeomin, Daxxify) coverable only under the medical benefit (as a provider-administered medication).

B. **Initial Authorization**:

1. For hyperhidrosis ONLY: When pre-authorization is approved, botulinum toxin type A shall be authorized in quantities of up to 2 injection treatments within a 24-week period.

2. For all other conditions (except as listed in 1 above): When pre-authorization is approved, botulinum toxin type A may be authorized in quantities up to 4 injection treatments within a 48-week period.

C. **Continued Authorization:**

1. After the initial authorization, up to 4 injection treatments over a 48-week period may be considered medically necessary if objective measures support clinical benefits from treatment.

2. Additional treatments may be authorized on a case-by-case basis if documentation of objective measures supporting the need for more frequent dosing are provided.

3. Coverage may be reviewed at least every 12 months to confirm that current medical necessity criteria are met and that the medication is effective, defined as sustained clinical improvement from reduced symptoms (such as pain and functional impairment).

V. Botulinum toxin type A (Botox, Dysport, Xeomin, Daxxify) is considered not medically necessary for skin wrinkles or other cosmetic indications.

VI. Botulinum toxin type A (Botox, Dysport, Xeomin, Daxxify) is considered investigational for all other indications, including, but not limited to:

- **A.** Allergic rhinitis.
- **B.** Benign prostatic hyperplasia.
- **C.** Congenital talipes equinovarus (clubfoot).
- **D.** Dermatochalasis (excessive eyelid skin, "baggy eyes").
- **E.** Dry eye disease.
- **F.** Headache, non-migraine (e.g. chronic daily, tension, cluster).
- **G.** Interstitial cystitis.
- **H.** Low back pain (LBP).
- **I.** Medication overuse headache (MOH).
- **J.** Motor tic disorder, chronic (including Tics associated with Tourette syndrome).
- **K.** Myofascial pain.
- **L.** Nerve entrapment or compression syndromes, other (those not listed in Section II Above: such as brachial plexus injury, carpal tunnel syndrome Piriformis syndrome).
- **M.** Obesity.
- **N.** Osteoarthritis (OA)-related pain, including of the knee.
- **O.** Plantar fasciitis pain.
- **P.** Temporomandibular dysfunction (TMJ), bruxism, and/or masseter muscle spasm.
- **Q.** Tennis elbow (lateral epicondylitis).
- **R.** Tremors [e.g. essential (benign) tremor, Parkinson's disease-related tremor].

Position Statement

- There are four botulinum toxin type A products available (abobotulinumtoxinA, daxibotulinumtoxinA, incobotulinumtoxinA, and onabotulinumtoxinA) that all work by inhibiting the release of acetylcholine from peripheral cholinergic nerve endings, thereby blocking the cholinergic transmission.
- The intent of this policy is to allow coverage for specific diagnoses where there is demonstrated safety and efficacy from clinical trials to support their use, including spasmodic conditions, and other specific indications. Coverage for hyperhidrosis is allowed when there is documentation the condition is persistent and severe and has resulted in significant medical complications. Coverage for migraine indications is allowed when lower-cost standard of care treatment alternatives are not effective.
- There is insufficient evidence to establish that one botulinum toxin A product is more effective at comparable doses.
- Botulinum toxin type A products are all produced using different methods, so their dosing and potencies are <u>not</u> the same (the number of units of one botulinum toxin type A product cannot be converted to units of another product).

- Conditions for which use of botulinum toxin type A may be considered medically necessary are based on evidence supported by well-designed randomized controlled trials.
- The evidence for use of botulinum toxin type A in chronic migraine headache is inconsistent. Use should be reserved for those who have trialed other treatment options.
- Use of botulinum toxin (all serotypes) for treatment of wrinkles or other cosmetic conditions is considered not medically necessary.
- Botulinum toxins (type A and type B) are being investigated in many different conditions where muscle tension is thought to play a role. The quality of evidence from the majority of these studies is poor because they lack controls, are not randomized or blinded, and only involve small numbers of subjects.

Summary

CLINICAL EFFICACY

Endoscopically-administered botulinum: Achalasia (primary), Gastroparesis, and Dysphagia

- Achalasia is an esophageal motility disorder, also known as cardiospasm, which results in increased lower esophageal sphincter tone, difficulty swallowing, and sometimes regurgitation and chest pain. [1]
- Pneumatic dilation is the preferred medical treatment option for primary achalasia. [2]
- One Cochrane review concluded that pneumatic dilation produces a higher remission rate at 6 and 12 months compared to botulinum toxin. [1]
- Standard therapies for gastroparesis include diet modification (smaller meals, more frequent meals, exacerbating food avoidance), use of promotility medications, (metoclopramide, cisapride, erythromycin), and/or removal/reduction of underlying causes of gastroparesis (such as opioids).
- Approach to treatment of dysphagia (non-achalasia) is dependent on underlying pathology but may include swallowing rehabilitation (such as by a speech or occupational therapist) and/or diet modification. [3]
- Several small, poor-quality trials studied onabotulinumtoxinA in the treatment of gastroparesis. Improvement in gastric emptying time was inconsistent with some trials showing possible benefit [4] and others showing no benefit. [5 6] Despite inconclusive benefit of onabotulinumtoxinA, there is a lack of robust evidence for management of refractory gastroparesis for any one treatment approach. Therefore, botulinum toxin A may be considered medically necessary when standard initial therapies are ineffective. [7]

Anal Fissures

- Nitroglycerin ointment, diltiazem cream, and onabotulinumtoxinA have been studied in the treatment of anal fissures.
    * Nitroglycerin ointment and topical calcium channel blocker (e.g. diltiazem or nifedipine) cream are the least invasive.
    * Several small studies suggest healing rates of up to 70% with onabotulinumtoxinA. [8]
    * Trials comparing nitroglycerin ointment with onabotulinumtoxinA show inconsistent results.

- A comparative trial demonstrated a healing rate of 52% with nitroglycerin compared to 24% with onabotulinumtoxinA after 2 weeks of treatment. [9]
- A second comparative trial demonstrated a healing rate of 60% with nitroglycerin ointment compared to 96% with onabotulinumtoxinA. [10]
- Another study in 73 subjects with anal fissure found there were no advantages of onabotulinumtoxinA over nitroglycerin ointment in fissure healing and fissure-related pain. [11]
- A Cochrane review concluded topical CCBs, nitroglycerin and botulinum toxin to be overall similarly effective non-surgical treatment options. However, surgical sphincterotomy remains the most efficacious therapy; however, it is limited by significant risks. [8]

* A small randomized, double-blind, controlled trial comparing diltiazem cream to onabotulinumtoxinA showed no difference in fissure healing between groups after three months of treatment. [12]

Congenital aganglionic megacolon (Hirschsprung disease)[13-16]

- Congenital aganglionic megacolon (Hirschsprung disease) is a rare gastrointestinal disorder, due to incomplete neuronal development in the distal colon, resulting in abnormal bowel function due to increased/decreased anal sphincter tone or withholding. The condition is generally diagnosed in children and can result in fecal incontinence, constipation, and enterocolitis.
- For constipation symptoms due to increased anal sphincter tone or withholding, treatment options include standard bowel regimen, botulinum toxin, and surgery. There is no standard sequencing of therapies; however, the goal of conservative therapies, including botulinum, includes avoidance of surgical procedures.

Cervical dystonia (spasmodic torticollis)

- Cervical dystonia (or spasmodic torticollis) is characterized by involuntary contractions of the neck muscles resulting in twisting and repetitive movements, and/or abnormal postures. [17]
- A Cochrane review concluded a significant decrease in the cervical dystonia severity scale (CDSS) along with an improved physician's global assessment score and reduction in pain after use of onabotulinumtoxinA injection relative to placebo. The CDSS is an objective measurement used to quantify the severity of abnormal head positioning that results from cervical dystonia. [17]
- OnabotulinumtoxinA has not been shown to be effective in the treatment of in chronic neck pain without torticollis (with or without cervicogenic headache) and mechanical neck disorders and whiplash. [18 19]

Migraine Headache

- The International Headache Society (IHS) Classification of Chronic Migraine Headache's definition of chronic migraine includes that headaches are present on 15 days or more per month, and that at least 8 of these episodes meet the criteria for pain and associated symptoms of migraine (*Appendix 1*).
- The U.S. Headache Consortium endorses headache calendars as the gold standard to track treatment progress. [20]

- Evidence supporting the efficacy of botulinum toxin A in the treatment of migraines has been inconsistent.[21]
- Collective results of seven randomized, controlled episodic migraine trials (totaling more than 1,000 patients) have failed to demonstrate a significant difference between botulinum toxin A and placebo in migraine prevention. Pre-specified primary endpoints and most secondary endpoints were not met. [22-26]
- Two additional trials studying onabotulinumtoxinA in the treatment of chronic migraine were more recently published. [27 28]
    * In the PREEMPT 1 trial, there was no difference between placebo and onabotulinumtoxinA in mean change in headache episodes, the primary endpoint.
    * In the PREEMPT 2 trial, the primary endpoint was changed to mean change in headache days after the PREEMPT 1 trial failed to meet its primary endpoint. A statistical difference favoring onabotulinumtoxinA over placebo was demonstrated. The mean number of headaches decreased from approximately 20 to 11 in the onabotulinumtoxinA group and from approximately 20 to 13 in the placebo group at week 24.
    * Subjects enrolled in the trials had migraine headaches occurring on 15 or more days per 4 weeks, of which each consisted of four or more hours of continuous headache.
- The American Academy of Neurology (AAN) 2016 guideline update supports the use of botulinum toxin type A products in the prevention or treatment of chronic migraine headaches[21]. The AAN Assessment of botulinum toxin A concludes that:
    * They are likely effective in chronic migraine headaches and should be offered as a treatment option to increase the number of headache-free days.
    * They are likely ineffective in treatment of episodic migraine and chronic tension-type headache

    .
- Both the AAN and the American Headache Society recommend limiting the use of abortive therapies for headache. These include over-the-counter (OTC) medications such as NSAIDS and acetaminophen, given the risk of developing medication overuse headache (MOH). Use of OTC abortives should be limited to no more than 14 days per month. In addition, use of butalbital-containing medications and opioids can increase sensitivity to pain. Use of these prescription abortives should be limited to no more than nine days per month (or two days per week). [29]

  Use of Oral Prophylactic Therapies [30 31]
    * Guidelines from the American Academy of Neurology and American Headache Society recommend select antiepileptic medications (divalproex or topiramate) and beta-blockers (propranolol, timolol, or metoprolol) as options that should be offered to patients requiring migraine prophylaxis, with the highest level of evidence to support their use.
    * Other medications that are “probably effective and should be considered” include tricyclic antidepressant (TCA) amitriptyline, selective serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine, atenolol and nadolol.

* Use of carbamazepine and a variety of select antihypertensives (candesartan, lisinopril, clonidine, guanfacine, or pindolol) are possibly effective; however, the many other prophylactic alternatives with higher-quality evidence should be used first.
* Many other medications, including but not limited to selective serotonin receptor inhibitors (SSRIs; e.g. fluoxetine, fluvoxamine), other SNRIs (e.g. duloxetine), other AEDs (gabapentin, lamotrigine, and oxcarbazepine), calcium channel blockers (CCBs; e.g. nicardipine, nifedipine, verapamil) and clonazepam, have been studied in migraine prophylaxis, but evidence supporting their efficacy is conflicting, inadequate, or negative (support the therapy is ineffective). [30 31]
* There is insufficient evidence directly comparing botulinum toxin A with other prophylactic therapies such as beta-blockers, antiepileptic medications, tricyclic antidepressants, calcitonin gene-related peptide (CGRP) monoclonal antibodies, or oral CGRP antagonists . [7]

Other Types of Headaches:

* Chronic Daily Headache (CDH): botulinum toxin A has not been shown to be effective in treatment or prevention of CDH.[21 23 32 33]
* Tension Headache: Current evidence is insufficient to permit conclusions regarding botulinum toxin type A products as prophylactic therapy in patients with chronic tension headaches refractory to pharmacologic therapy. [21 22 34-37]
* Current evidence is insufficient to allow the use of botulinum toxin A in the treatment of episodic migraine headaches, tension headaches, or chronic daily headaches [21 34 36-38]

Hyperhidrosis

- Hyperhidrosis can lead to medical complications, including skin maceration with recurrent bacterial or fungal infection requiring treatment or persistent eczematous dermatitis. [39]
- Palmar hyperhidrosis can interfere with ability to function, when grip is impaired due to hyperhidrosis. [39]
- Topical treatments, such as aluminum chloride solution (Drysol) are the primary therapy for axillary and palmar hyperhidrosis, once secondary causes of hyperhidrosis are ruled out. Topical treatments and systemic anticholinergics are primary therapy for persistent eczematous dermatitis. [39]
- There are several double-blind trials that evaluate onabotulinumtoxinA in patients with primary axillary and primary palmar hyperhidrosis. [7 40 41]
  * Treated palms with onabotulinumtoxinA were associated with a 26% reduction in sweating (measured by ninhydrin sweat testing) compared to no reduction with placebo. [40]
  * In two pivotal trials, 81% to 91% of patients treated for primary axillary hyperhidrosis achieved a greater than 50% reduction in axillary sweating at 4 weeks compared with 36% to 41% in the placebo group. [7]
- The median duration of effect in two pivotal trials that evaluated onabotulinumtoxinA in primary axillary hyperhidrosis was 201 days. [7]

- Reduction in sweating is also described in case series reports for both palmar and axillary hyperhidrosis with onabotulinumtoxinA injections lasting up to 5-12 months. [42 43]
- However, despite the reduction in sweating, onabotulinumtoxinA does not affect the unpleasant odor.
- In a small case study, intracutaneous onabotulinumtoxinA was effective in ceasing gustatory sweating up to a mean duration of 17 months. [44]

Muscle Spasms and Dystonias

- A spasm is defined as a sudden involuntary contraction of one or more muscles.
- Muscle spasms are a potential symptom of spasticity, a condition in which specific muscles are continuously contracted. The contraction causes muscles to be stiff or tight and may interfere with movement, speech, and walking.
- Botulinum has been studied and shown to be effective in spasticity due to cerebral palsy,[45 46] spastic hemiplegia or paraplegia,[47] dysphonia,[7 48], blepharospasm,[49] hemifacial spasm,[50] facial nerve disorders, and demyelinating disease of the CNS,[7 51], as well as a variety of dystonias: hand dystonia, [7] oromandibular dystonia,[7] spasmodic torticollis,[7] and torsion dystonia [7].

Pelvic Floor Dysfunction, including levator (pelvic floor) spasm

- Pelvic floor dysfunction is global term used to describe a number of conditions, including chronic pelvic pain. For pelvic floor dysfunction due to levator (pelvic floor) muscle spasm, non-pharmacologic therapy includes physical therapy with pelvic floor training can be used, along with other types of physical therapy. Pharmacologic therapies include various chronic pain medications such as antiepileptics, antidepressants (tricyclic, serotonergic), muscle relaxants, NSAIDs, as well as hormone replacement therapies. Opioids may be used for severe pain, along with trigger point injections. Surgery is reserved for refractory pain. [52]
- The evidence for onabotulinumtoxinA for treatment of pelvic floor muscle spasm is limited to one randomized controlled trial (n=60). The trial reported a decrease in pelvic floor muscle pressure but no significant difference reduction in pain scores.[52] However, there is a lack of robust evidence for management of refractory pelvic floor muscle spasm for any one treatment approach. Therefore, botulinum toxin A may be considered medically necessary when standard initial therapies are ineffective.

Raynaud's Disease

- Raynaud's phenomenon (Raynaud disease) is vasospasm due to cold or stress and can lead to severe constriction of the digits (both fingers and toes). Severe cases may result in digital ischemia, ulcers, and gangrene. [53]
- Non-pharmacologic therapy includes trigger avoidance, including cold, vasoconstricting medications, and smoking. Pharmacologic therapies may be used for refractory RP.
- Dihydropyridine calcium channel blockers (CCBs), such as amlodipine or nifedipine, are the usual first-line pharmacologic treatment options. Other pharmacologic treatment options include various vasodilators: phosphodiesterase (PDE) type 5 inhibitor (e.g. sildenafil, tadalafil), topical nitroglycerin, an angiotensin receptor blocker (e.g. losartan, valsartan), or a serotonin reuptake inhibitor.

- There is limited evidence to guide the management of refractory or progressive ischemia. The goal is prevention of tissue loss, including amputation of digits. Treatment may include aggressive non-pharmacologic, pharmacologic, and surgical therapies. [54]
- The evidence for onabotulinumtoxinA or incobotulinumtoxinA for treatment of Raynaud's syndrome is limited to one pilot trial and one retrospective case series with onabotulinumtoxinA. [88-90] However, given the lack of non-surgical options for refractory ulcers, botulinum toxin A may be covered when standard vasodilator therapy is ineffective, not tolerated, or all options are documented as medically contraindicated.

Sialorrhea (drooling)

- Botulinum toxin A or B can be used for reduction of sialorrhea in patients with a variety of neurological disorders. The goal of therapy is to reduce sialorrhea -associated complications, such as aspiration pneumonia or skin breakdown.
- Anatomically guided injections of rimabotulinumtoxinB into the parotid and submandibular glands appear to effectively improve sialorrhea in patients with a variety of neurologic conditions, including Parkinson's disease and amyotrophic lateral sclerosis (ALS). [7 55 56]

Thoracic Outlet Syndrome

- Thoracic outlet syndrome (TOS) is a form of myofascial pain and may include brachial plexus injury.
    * A Cochrane review concluded that there is insufficient evidence to conclude that botulinum toxin is effective for treatment of TOS. [57] In one small trial, botulinum toxin did not significantly reduce pain or disability scores versus placebo in patients with TOS (of any type). The evidence is complicated by a lack of consensus in the diagnosis of TOS. Additional research is needed to clarify the benefit of TOS treatments.[58]
    * Strengthening exercises, physical therapy and surgery are the standard of care. In patients, in whom these options have been ineffective, botulinum toxin may be a treatment option.

Urinary Incontinence - Neurogenic and idiopathic detrusor overactivity/detrusor hyperreflexia

- Several open-label studies (n=15 to n=200) demonstrated an increase in bladder capacity, a decrease in bladder pressure, and a decrease in incontinence episodes after injection with onabotulinumtoxinA, in both children and adults.[59-61]
- A Cochrane review concluded both botulinum type A and B formulations are effective treatment options for urinary incontinence due to refractory detrusor overactivity due to neurogenic or idiopathic overactive bladder (OAB). [62]

Refractory Postherpetic Neuralgia (PHN) [63]

- Refractory postherpetic neuralgia (PHN) refers to pain that persists after an acute episode of herpes zoster and resolution of the rash. PHN affects nerve fibers and skin and is characterized by constant burning, stabbing sensation or pain triggered by light contact with non-painful stimuli, resulting in decreased quality of life.
- First-line pharmacologic therapies for PHN include topical lidocaine, gabapentinoids (gabapentin, pregabalin), tricyclic antidepressants (TCAs; amitriptyline, nortriptyline), and serotonin-norepinephrine reuptake inhibitors (SNRIs; duloxetine and venlafaxine).

- A systematic review and meta- analysis of seven trials with a total of 752 patients concluded that botulinum toxin A has a greater efficacy than lidocaine for postherpetic neuralgia, based on the visual analog scale (VAS) of these 7 trials. [64]
- For refractory PHN, in which first-line standard of care pharmacologic treatment options have been ineffective, botulinum toxin A may be a treatment option for these patients.

INVESTIGATIONAL USES

Allergic Rhinitis

- One small (n=34) randomized controlled trial of 8-week duration suggests efficacy of onabotulinumtoxinA in relieving rhinorrhea, nasal obstruction and sneezing due to allergic rhinitis. There was no difference between onabotulinumtoxinA and placebo groups for the symptom of itching. [65]
- Well-designed, large-scale trials with repeated injections and comparison to nasal steroids are necessary to validate positive benefits of using onabotulinumtoxinA in this condition.

Benign Prostatic Hyperplasia (BPH)

- A small, poor-quality trial comparing the effects of onabotulinumtoxinA with or without an alpha-adrenergic antagonist suggest possible onabotulinumtoxinA efficacy. The absence of a placebo comparator makes it difficult to determine the true efficacy of onabotulinumtoxinA. [66] The evidence for the use of onabotulinumtoxinA in the treatment of BPH is limited to a variety of Phase II and uncontrolled trials. [7 67] Additional higher-quality studies are needed before onabotulinumtoxinA can be considered safe and effective in this condition.

Congenital talipes equinovarus (clubfoot) [68]

- A Cochrane review concluded that there is insufficient evidence to conclude that botulinum toxin is effective for treatment of clubfoot. The evidence is limited to one small trial, as adjunctive therapy to casting.
- Usual conservative interventions include stretching, casting, and splinting. Surgery is reserved for resistant deformities.

Dermatochalasis

- Dermatochalasis is a condition in which a fold of skin develops in the eyelid, potentially leading to impaired vision, blepharitis, and dermatitis. Surgery is the current standard of care.
- A small, poor-quality study (open-label study without a placebo comparator) suggests that onabotulinumtoxinA may be an effective treatment for upper eyelid dermatochalasis. [69] Additional well-controlled studies are needed before onabotulinumtoxinA can be considered safe and effective in this condition.

Dry Eye Disease

- The evidence for the use of onabotulinumtoxinA for dry eye disease is limited to one small pilot trial (n=20). [70] Larger, well-controlled trials are needed to establish safety and effectiveness of onabotulinumtoxinA for this indication.

Interstitial Cystitis

- Four, poor-quality studies (case series) have assessed onabotulinumtoxinA treatment for pain and improvement of bladder capacity in patients with interstitial cystitis. All

reports suggest efficacy, though results have not been confirmed in larger controlled trials. [7 71]

Low Back Pain

- The evidence for the use of botulinum toxin A in the treatment of lower back pain is limited to several small, poor-quality trials. [72] The studies did not address functional improvement or long-term effects of onabotulinumtoxinA. Large, well-controlled studies are needed before onabotulinumtoxinA can be considered safe and effective in this condition. [7]

Motor Tics

- In one small, poor-quality trial, onabotulinumtoxinA reduced tic frequency and urge in patients with Tourette Syndrome or Chronic Tic Disorder. [73] These reductions were not associated with an overall clinical benefit (measured by the patient's global impression of change).

Myofascial Pain

- OnabotulinumtoxinA has not been shown to provide a consistent benefit over placebo in the treatment of myofascial pain. [7 74]
- One small trial found botulinum toxin A improved pain and quality of life. However, small trial size and use of an enriched protocol design limit generalizability of findings to clinical practice. Only half of patients responded to the initial dose of botulinum toxin A and were enrolled in the randomized phase of the trial. [75]

Obesity

- There is no reliable evidence that onabotulinumtoxinA is useful in reducing body weight in obese patients.
    * Two small, poor-quality trials failed to show a reduction in body weight after administration of onabotulinumtoxinA. [76 77]
    * A small randomized, double-blind study in 24 morbidly obese patients demonstrated significant difference between onabotulinumtoxinA and saline. However, patients were also maintained on a liquid diet for eight weeks. [78]

Orthopedic Pain – Plantar Fasciitis, Lateral epicondylitis (tennis elbow), Osteoarthritis (OA) of the knee

- Four small, exploratory randomized controlled trials reported an improvement in pain scores with onabotulinumtoxinA in patients with plantar fasciitis refractory to other therapies. [79-82]
- Several small, poor-quality trials evaluated onabotulinumtoxinA in patients with lateral epicondylitis (tennis elbow). [83-85] Consistent benefit has not been demonstrated across trials.
- One trial evaluated intra-articular onabotulinumtoxinA for treatment of OA-related knee pain. [86] Despite a reduction in pain with onabotulinumtoxinA versus placebo, additional evidence is needed to establish the clinical benefit versus established standard of care treatments for OA, such as NSAIDs.
- Larger, well-controlled trials are needed to establish safety and effectiveness in these conditions and to establish efficacy relative to conventional therapies. [7]

Nerve Entrapment and Compression Syndromes (such as Brachial Plexus Injury, Carpal Tunnel Syndrome, Piriformis Syndrome)

- Piriformis syndrome is a form of myofascial pain characterized by sciatica and buttock tenderness.
    * Few case reports describe the management of piriformis syndrome. [87] Physical therapy, steroid injections, surgical dissection or resection of the muscle have been reported to relieve symptoms.
    * Well-designed studies using onabotulinumtoxinA for this condition have not been conducted. Available evidence consists of small (fewer than 30 patients) open-label, uncontrolled studies. [7 88]
- There is insufficient evidence to establish efficacy of botulinum toxin for treatment of carpal tunnel syndrome. The evidence is limited to one pilot trial. [89]

Temporomandibular dysfunction (TMJ), Bruxism, and/or Masseter Muscle Spasm and Hypertrophy

- Several small, uncontrolled (case series) studies have studied onabotulinumtoxinA in the treatment of symptoms (headache, jaw dislocation, etc.) arising from TMJ dysfunction. Larger, well-controlled studies are needed to establish benefit in the treatment of this condition. [90-93]
- Several small, poor-quality trials evaluated onabotulinumtoxinA in patients with bruxism, masseter muscle spasm, and/or masseter hypertrophy and one small trial with incobotulinumtoxinA. Consistent benefit has not been demonstrated across trials. Additional larger trials are needed to establish the safety and efficacy of botulinum toxin type A. [94-98]

Tremor

- There is insufficient evidence to support the use of onabotulinumtoxinA in essential hand tremor or MS-related tremor and no evidence in Parkinson's disease-related tremor. [7 99]
- OnabotulinumtoxinA resulted in significant improvement of postural, but not kinetic essential hand tremors. [99] Likewise, one small crossover trial of incobotulinumtoxinA (n=30) improved rest tremor, tremor severity, and postural tremor. [100] However, there is not compelling evidence that either botulinum toxin formulation leads to better functional efficacy for patients.

SAFETY

- The severity and type of adverse effects depends on the location where the botulinum toxin A is injected, the dose used, and the injection technique.
- Commonly reported adverse events observed in clinical trials of onabotulinumtoxinA include dry mouth, dysphagia, asthenia, diplopia, and injection site pain. The prevalence and severity of adverse effects may vary depending on the dose and the site of injection. [51]
- All botulinum toxin products carry a box warning in their labeling describing the potential for toxin to spread from the site of injection and produce symptoms consistent with botulinum toxin effects. Symptoms may include asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence and breathing difficulties and may occur hours to weeks after injection.

Swallowing and breathing difficulties can be life threatening. Deaths have been reported.

- The safety, efficacy and dosing of botulinum toxins has not been established for any condition in children less than 12 years of age.

DOSING CONSIDERATIONS

- Botulinum toxin type A products are all produced using different methods, so their dosing and potencies are not the same (the number of units of one botulinum toxin type A product cannot be converted to units of another product).
- Starting doses for botulinum toxin type A products are available in the prescribing information for the specific products. Follow-up doses may be adjusted based on the effectiveness of the initial injections and adverse effects.

Appendix 1: International Headache Society Classification of Chronic Migraine Headache [101]

A. Headache (tension-type and/or migraine) on 15 or more days per month for at least 3 months.*

B. Occurring in a patient who has had at least 5 attacks fulfilling criteria for a migraine without an aura.

C. On 8 or more days per month for at least 3 months headache has fulfilled criteria for pain and associated symptoms of migraine without aura in either or both of criteria 1 head 2 below:

1. At least two of the following criteria a, b, c, and d below are met:

a) Unilateral location.

b) Pulsating quality.

c) Moderate or severe pain intensity.

d) Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs).

AND at least one of the following criteria e or f below are met:

e) Nausea and/or vomiting.

f) Photophobia and phonophobia.

2. Treated and relieved by triptan(s) or ergot before the expected development of the above symptoms.

D. No medication overuse and not attributed to another causative disorder.

* Characterization of frequently recurring headache generally requires a headache diary to record information on pain and associated symptoms day-by-day for at least one month. Sample diaries are available at http://www.i-h-s.org.

Cross References
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BlueCross BlueShield Association Medical Policy, 8.01.19 - Treatment of Hyperhidrosis. [July 2023]
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Oral CGRP antagonists and 5-HT 1f agonists, Medication Policy Manual, Policy No. dru635
CGRP Monoclonal Antibodies, Medication Policy Manual, Policy No. dru540
Cosmetic and Reconstructive Surgery, Medical Policy Manual; Surgery, Policy No. 12.
Gender-Affirming Care Products, Medication Policy Manual, Policy No. dru757

Codes	Number	Description
HCPCS	J0585	Injection, onabotulinumtoxinA (Botox), 1 unit
HCPCS	J0586	Injection, abobotulinumtoxinA (Dysport), 5 Units
HCPCS	J0588	Injection, incobotulinumtoxinA (Xeomin), 1 unit
		Injection, daxibotulinumtoxinA (Daxxify)

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Revision History

Revision Date	Revision Summary
12/7/2023	• Added newly approved Daxxify (daxibotulinumtoxinA) to policy. • Simplified chronic migraine criteria for operational consistency. • Updated step therapy for chronic migraines requiring only one step of prior chronic migraine treatment. • Updated reauthorization to 12 months for migraines. • Added updated AAN 2016 guideline statement.
12/9/2022	• Policy criteria language updated for the following (no change to intent): - Congenital aganglionic megacolon (Hirschsprung disease): clarified symptom severity - Migraine headaches: explicitly added oral CGRP antagonist step therapy. - Urinary incontinence, due to detrusor overactivity: added Myrbetriq (mirabegron) as an acceptable step therapy. • Added coverage criteria for refractory postherpetic neuralgia (PHN) after standard of care treatments.
1/20/2021	• Updated COT language. • Added coverage criteria for thoracic outlet syndrome (TOS) in patients with functional impairment. • Updated criteria for hyperhidrosis: - Clarified that secondary infection or skin maceration are considered separate complications. Added inability to satisfy demands of employment as an example of a complication. - Updated step therapy requirements. - Added a requirement that antiperspirant or anticholinergics (topical or oral) have been tried • Clarified initial and continued authorization periods. Re-authorization criteria were aligned for all indications. Re-authorization requires documentation of clinical benefit and up to 4 doses in a 48-week period may be covered. More frequent doses may be covered on a case-by-case basis.
10/28/2020	Clarified migraine criteria, including removal of duplicative criteria.
4/22/2020	• Clarified CGRP monoclonal antibody step therapy for migraines (when used for prophylaxis). CGRPs used as abortive therapy do not meet this criterion. • Added coverage criteria for refractory Raynaud's and pelvic floor dysfunction. • Policy criteria updated for achalasia: simplified coverage to use as part of an endoscopic procedure for upper GI diagnoses.

Revision Date	Revision Summary
1/22/2020	• Added continuation of therapy (COT) criteria (no change to intent of coverage criteria). • Clarified reauthorization (simplified; no change to intent). • Policy criteria updated for migraine indication to include CGRP monoclonal antibody as step therapy option.
1/31/2019	• Simplified Section I criteria. • Updated investigational uses: - Removed Migraine headache (chronic) in combination with CGRP inhibitors from investigational uses. - Clarified pelvic floor spasm (including pelvic pain, vulvodynia, and vaginismus). • Clarified reauthorization criteria for Section II.
8/17/2018	Added as Investigational uses: Migraine headache (chronic) in combination with CGRP inhibitors.
1/19/2018	• Updated migraine severity criteria to International Headache Society (HIS) standard. • Updated list of Investigational uses (add Dry Eye Disease and OA-related knee pain).
2/17/2017	• The policy criteria were simplified for hyperhidrosis. • Added coverage criteria for congenital aganglionic megacolon (Hirschsprung disease). • Clarified quantity limits to 2 doses per 24-weeks and 4 doses per 48-weeks (versus use of 6 and 12 months, respectively).
2/12/2016	• The policy criteria were updated for hyperhidrosis to clarify the wording regarding medical complications for the definition of medical necessity. • Added coverage criteria for lower limb dystonia, a new FDA-indication. • Added as Investigational uses: dysphagia (non-achalasia), Raynaud's disease, and bruxism/masseter muscle hypertrophy.
1/1/1996	New policy.

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Medication Policy Manual

Policy No: dru020

Topic: Immune Globulin Replacement Therapy, (IVIG, SCIG):

- Alyglo
- Asceniv
- Bivigam
- Cutaquig
- Cuvitru
- Flebogamma DIF
- Gammagard
- Gammagard S/D
- Gammaked
- Gammaplex
- Gamunex-C
- Hizentra
- Hyqvia
- Octagam
- Panzyga
- Privigen
- Xembify

Date of Origin: January 1996

Committee Approval Date: September 19, 2024

Next Review Date: 2024

Effective Date: January 1, 2025

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Intravenous immune globulin (IVIG) and subcutaneous immune globulin (SCIG) are preparations containing antibodies purified from human blood. They are used in the treatment of many different conditions resulting from immune deficiencies or other immunologic conditions.

Policy/Criteria

Most contracts require pre-authorization approval of immune globulins prior to coverage.

I. Continuation of therapy (COT) **and** new starts (treatment-naïve patients): The use of Higher-Cost Immune Globulin Replacement Products (as listed in *Table 2*) is considered not medically necessary.

II. Continuation of therapy (COT): All other immune globulins (as listed in *Table 1*) may be considered medically necessary for COT when criterion A, B, or C **AND** D below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

AND

D. Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, *Site of Care Review*, dru408].

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

III. New starts (treatment-naïve patients): All other immune globulins (as listed in *Table 1*) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A and B below are met.

A. Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, *Site of Care Review*, dru408].

AND

B. At least one of the following diagnostic criteria 1 through 5 below is met:

1. Immunodeficiency (primary or acquired), diagnosed by, or in consultation with an immunologist or hematologist, as defined in criterion a or b:

a. A diagnosis of one of the following and documented **hypogammaglobulinemia** (a low baseline serum IgG level):

i. Primary humoral immunodeficiency diseases (PID) (as defined in *Appendix 1*).

ii. HIV infected children (< 13 years of age) with hypogammaglobulinemia.

iii. Hematologic malignancy-related hypogammaglobulinemia.

iv. Post-allogeneic bone marrow transplant (BMT).

v. B-cell mediated cancer [e.g., chronic lymphocytic leukemia (CLL), B-cell lymphoma].

vi. Hypogammaglobulinemia in neonates, with a low birth weight (less than 1500g) or in a setting with high baseline infection rate or morbidity.

OR

b. A diagnosis of **dysgammaglobulinemia**, primary or due to multiple myeloma in patients with stable disease, and at least one of the following:

i. high risk of recurrent infections despite prophylactic antibiotic therapy.

ii. poor IgG response to the pneumococcal vaccine.

iii. low normal IgG levels during acute sepsis episodes.

OR

2. Hematologic disorders (immune-mediated), not responding to alternative therapies, or at high risk of bleeding:

a. Acquired Factor VIII inhibitor, diagnosed by, or in consultation with an immunologist or hematologist, and when conventional therapy is ineffective or not tolerated. (e.g., immunosuppressive therapy with cyclophosphamide, steroids, or azathioprine).

OR

b. **Autoimmune hemolytic anemia** (AIHA), diagnosed by, or in consultation with an immunologist or hematologist, and not responding to alternative therapies (e.g., steroids, immunosuppressive agents, plasmapheresis, rituximab and/or splenectomy).

OR

c. **Fetal (neonatal) alloimmune thrombocytopenia** (FAIT) diagnosed by, or in consultation with a neonatologist, hematologist, or obstetrician, and with documented diagnosis.

OR

d. **Idiopathic thrombocytopenia purpura**, also known as "immune thrombocytopenia," (acute; ITP), when a rapid increase in platelet count is necessary, such as in an acute bleeding episode or prior an invasive procedure (including surgery, epidural anesthesia, or Cesarean section).

OR

e. **ITP (chronic)**, diagnosed by, or in consultation with an immunologist or hematologist, and when the platelet count is dangerously low, defined as a platelet count less than 30,000 cells/mm3 in children, less than 20,000 cells/mm3 in adults, or less than 30,000 cells/mm3 along with signs/symptoms of bleeding in adults, as a bridge to an alternative chronic therapy (including but not limited to rituximab, a TPO mimetic, or splenectomy) OR when at least one other chronic therapy has been ineffective or all are contraindicated.

OR

f. **ITP in pregnancy**, diagnosed by, or in consultation with a neonatologist, hematologist, or obstetrician, and when at least one of the following criteria are met:

i. Platelet counts less than 20,000/mm3 in the third trimester, despite an adequate course of corticosteroids, unless use of steroids are contraindicated, or not tolerated.

OR

ii. Platelet counts less than 30,000/mm3 associated with bleeding or before vaginal delivery or C-section.

(For IVIG use in preparation for C-section or epidural anesthesia, see criteria 2.d. above)

OR

g. **Post-transfusion purpura** (hemolytic transfusion reaction) in severely affected patients.

OR

h. **Pure red cell aplasia** (PRCA, viral) diagnosed by, or in consultation with an immunologist or hematologist, and with documented parvovirus B19 infection and severe anemia.

OR

3. **Neuromuscular disorders,** diagnosed by, or in consultation with a neurologist, dermatologist or rheumatologist, AND there is clinical documentation (including, but not limited to chart notes) of significant functional impairment:

a. **Guillain-Barré syndrome** (GBS), including **Acute inflammatory demyelinating polyneuropathy** (AIDP), when one of criteria i through iv below are met:

i. Deteriorating pulmonary function tests.

OR

ii. Rapid deterioration with symptoms for less than 2 weeks.

OR

iii. Rapidly deteriorating ability to ambulate.

OR

iv. Inability to walk independently for 10 meters.

OR

b. **Chronic inflammatory demyelinating polyneuropathy** (CIDP) when both criteria i and ii below are met:

i. Significant functional disability.

AND

ii. Documentation of slowing of nerve conduction velocity on electromyogram (EMG)/ nerve conduction study (NCS).

OR

c. **Acute demyelinating encephalomyelitis** (ADEM) or **anti-NMDA receptor encephalitis** when prior therapy with corticosteroids has been ineffective or not tolerated.

OR

d. **Lambert-Eaton myasthenic syndrome** (LEMS**)**.

OR

e. **Multifocal motor neuropathy** (MMN) in patients with conduction block [partial (>30%) or complete block].

OR

f. **Myasthenia gravis (MG)**, when criteria i. and ii. below are met:

i. For the treatment of acute crisis (e.g., respiratory failure, swallowing difficulties) **OR** chronic decompensation

AND

ii. Documentation that at least ONE other standard MG treatment is ineffective or not tolerated [such as plasmapheresis/ plasma exchange (PLEX), pyridostigmine (generic, Mestinon), non-steroidal immunomodulating therapies (such as azathioprine, cyclosporine, mycophenolate, tacrolimus, methotrexate, or cyclophosphamide)].

OR

g. **Paraneoplastic opsoclonus ataxia syndrome** (Opsoclonus-myoclonus ataxia syndrome, OMS) in pediatric neuroblastoma patients with significant functional impairment and not responding to an adequate course of steroids (at least 3 to 7 days).

OR

h. **Pemphigoid, refractory immunobullous disease** (e.g., bullous pemphigoid, pemphigus foliaceus, pemphigus vulgaris) until conventional treatment takes effect (e.g., immunosuppressive agents and plasmapheresis).

OR

i. **Refractory myositis**, including but not limited to autoimmune myositis, **dermatomyositis** (adult), or polymyositis, in patients with severe active illness including muscle weakness and associated severe disability when corticosteroids or other immunosuppressants (e.g., azathioprine, methotrexate, or cyclophosphamide) have been ineffective, are contraindicated or not tolerated.

OR

j. **Juvenile Dermatomyositis** (JDM), with muscle weakness and associated severe disability, with at least ONE of the following documented diagnostic criteria below:

i. Evidence of myositis, demonstrated by abnormality of muscle biopsy, MRI, OR EMG.

OR

ii. Increased muscle enzymes levels (such as CPK, AST, LDH, and/or aldolase)

OR

iii. Cutaneous changes, including heliotrope dermatitis (rash on the upper eyelids) and Gottron's papules (papules over the knuckles), not responding to oral corticosteroids, methotrexate, and/or another oral immunosuppressant.

OR

k. **Stiff-Person Syndrome** when treatment with other agents is ineffective or not tolerated. (e.g., diazepam, baclofen, clonazepam, valproic acid, and clonidine).

OR

l. **Systemic lupus erythematosus,** for severe active disease when other interventions are ineffective or not tolerated (e.g., corticosteroids and immunosuppressive agents, such as cyclophosphamide or azathioprine).

OR

4. **Transplant (solid organ), antibody (Ab)-mediated rejection,** diagnosed by, or in consultation with a transplant specialist or immunologist, and criteria a or b below are met**:**

a. **<u>Prevention</u> of antibody (Ab)-mediated rejection**: Prior to solid organ transplant and in the peri-operative period, for patients at high risk for Ab-mediated rejection, including highly sensitized patients, and those receiving an ABO-incompatible organ.

OR

b. **<u>Treatment</u> of antibody-mediated rejection (a.k.a. vascular rejection, humoral rejection)**: Following solid organ transplant and confirmed by either biopsy or presence of panel reactive antibodies (PRAs).

OR

5. **Other Miscellaneous conditions** when criteria are met:

a. **Kawasaki syndrome**, diagnosed by, or in consultation with a subspecialist (pediatrician, cardiologist, or rheumatologist), and IVIG is used during the first ten days of diagnosis.

OR

b. **Pediatric intractable epilepsy,** diagnosed by, or in consultation with a neurologist, in candidates for surgical resection or when other interventions are ineffective or not tolerated. Examples of other interventions include, but are not limited to, anticonvulsant medications, ketogenic diets, and steroids. [85]

OR

c. **Post-Exposure prophylaxis against varicella-zoster** (VZV) in high-risk populations (immunocompromised individuals who lack evidence of immunity to VZV, pregnant women who lack evidence of VZV immunity, newborns of mothers who develop peri-partum varicella, or infants in the first two weeks of life), diagnosed by, or in consultation with a subspecialist (such as obstetrician, pediatrician, or infectious diseases specialist).

OR

d. **BK Viremia** (BK polyomavirus in solid organ transplantation), diagnosed by, or in consultation with a transplant or infectious diseases specialist, in patients with persistent viremia despite a sufficient reduction of immunosuppressive therapy for at least 4 **weeks.**

['Sufficient reduction' is defined as discontinuation of an antimetabolite (such as mycophenolate mofetil or azathioprine) OR a 50% dose reduction of a calcineurin inhibitor (such as tacrolimus or cyclosporine)].

OR

e. **PANDAS/PANS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections or Pediatric Acute-onset Neuropsychiatric Syndrome),** when the following (i, ii, iii, and iv) are met:

i. The patient is less than 18 years of age.

AND

Pediatric subspecialist assessment: The diagnosis is made by, or in consultation with, ONE of the following pediatric subspecialists (for an adolescent, consultation may be with an adult subspecialist): pediatric neurologist, pediatric psychiatrist, neurodevelopmental pediatrician, pediatric rheumatologist, pediatric allergist/immunologist.

NOTE: IVIG for adults with PANDAS/PANS is not coverable.

AND

ii. If the prescriber is not a pediatric subspecialist (e.g., primary care), clinical documentation must be provided that the pediatric subspecialist agrees with the treatment plan for IVIG [attestation].

AND

iii. Documentation of baseline evaluation, including details of neuropsychiatric symptoms, temporal relationship to the symptoms, and associated functional impairment.

NOTE: This evaluation must include clinical testing with a validated instrument, which must be performed pretreatment and posttreatment to demonstrate clinically meaningful improvement (See Appendix 2).

AND

iv. Step therapy: A clinically appropriate trial of at least **two** of the following (1, 2, 3, and/or 4.) are ineffective, not tolerated, or use of all are contraindicated, and documentation stating the therapies were specifically used

for PANDAS/PANS symptoms.

['Ineffective' is defined as a lack of sustained clinically meaningful improvement on a validated instrument in relation to the primary symptom complex]

1. *Antimicrobial therapy*: Short-course antibiotic therapy (such as amoxicillin, azithromycin, or penicillin) for a confirmed group A beta-hemolytic *Streptococcus* (strep) infection.

OR

2. *Anti-inflammatory therapy* with at least one of the following (criteria a, b, or c):

a. Nonsteroidal anti-inflammatory drugs (NSAIDs) for at least five days

OR

b. Systemic corticosteroids

OR

c. Plasma exchange (PLEX)

OR

3. *Psychoactive therapy* with at least one of the following (criteria a or b):

a. Selective serotonin reuptake inhibitors (SSRIs)

OR

b. Behavioral therapy (such as cognitive behavioral therapy [CBT])

OR

4. Tonsillectomy and/or adenoidectomy

IV. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers immune globulins coverable only under the medical benefit (regardless of self- or provider-administration).

B. When pre-authorization is approved, immune globulins (as listed in *Table 1*) will be covered in the quantities and for the authorization periods outlined in *Table 3*.

C. Although the use of specific high-cost immune globulin products (as listed in *Table 2*) is considered 'not medically necessary,' if pre-authorization is approved, these immune globulins (as listed in *Table 2*) will be covered:

1. In the quantities and for the authorization periods outlined in *Table 3*.

AND

2. Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, Site of Care Review, dru408].

D. Subcutaneous administration of immune globulin (SCIG) is considered an alternative to intravenous administration of immune globulin (IVIG) and may be considered medically necessary when one of the coverage criteria above is met.

E. For dose requests above the policy limits (as listed in *Tables 1, 2,* and *3*):

1. **IVIG:** Higher doses may be coverable for patients who have clear clinical documentation, including but not limited to chart notes, supporting an objective improvement in symptoms or function while treated with IVIG 2 g/kg per four weeks (or equivalent), and who have maximized adjunctive therapy, but continue to have functional impairment or incomplete disease control.

2. **SCIG:** Doses of SCIG in excess of those listed in *Tables 1 and 2* are considered 'not medically necessary.'

F. The concomitant use of maintenance SCIG and IVIG is considered not medically necessary.

Table 1. Coverable Immune Globulin Replacement Products

Product Name		Route of Administration	Coverable Dose
Carimune NF Flebogamma DIF Gammagard S/D	Octagam Privigen	IVIG	2 grams/kg per 4 weeks (or equivalent)
Gammagard Gammaked	Gamunex C	IVIG or SCIG	2 grams/kg per 4 weeks (or equivalent)
Cutaquig Hyqvia	Xembify	SCIG	2 grams/kg per 4 weeks (or equivalent)
Hizentra		SCIG	0.4 gm/kg per week (or equivalent)

Table 2. 'Not Medically Necessary' Higher-Cost Immune Globulin Replacement Products

Product Name		Route of Administration	Coverable Dose
Alyglo Asceniv Bivigam	Gammaplex Panzyga	IVIG	2 grams/kg per 4 weeks (or equivalent)
Cuvitru		SCIG	2 grams/kg per 4 weeks (or equivalent)

Table 3. Quantity Limits and Authorization Period

Indication [a]	Dosing Schedule
	[a] Hizentra may be authorized up to 0.4 gm/kg/week
Replacement Therapy - Immunodeficiency [with documented hypogammaglobulinemia (low IgG levels) or poor immune response (dysgammaglobulinemia)]	
Primary humoral immunodeficiency disease (PID)	- **Initial Authorization and Continued Authorization:** Up to 2 g/kg per four weeks. - Authorization **may** be reviewed at least every 12 months. - **Reauthorization:** Clinical documentation (including, but not limited to chart notes) must be provided to confirm that the medication is effective, defined as decreased occurrence of infections or normalization of IgG levels. - IVIG doses higher than 2 g/kg per four weeks may be considered when there is documentation of continued severe infections despite IVIG doses of 2 g/kg per 4 weeks. Higher doses of SCIG are not coverable.
Hematologic malignancy-related hypogammaglobulinemia (e.g., CLL, post-BMT)	
HIV+ children with hypogammaglobulinemia	
Hypogammaglobulinemia in neonates	
Hematologic disorders (immune-mediated)	
Acquired Factor VIII Inhibitor	- **Initial Authorization and Continued Authorization:** Up to 2 g/kg per four weeks. - Authorization **shall** be reviewed at least every 52 weeks. - **Reauthorization:** Clinical documentation (including, but not limited to chart notes) must be provided to confirm that the medication is effective, defined as initial response, and continued presence of Factor VIII inhibitor.
Autoimmune hemolytic anemia, (AIHA)	- **Initial Authorization and Continued Authorization:** Up to 2 g/kg per four weeks. - Authorization **shall** be reviewed at least every 52 weeks. - **Reauthorization:** Clinical documentation (including, but not limited to chart notes) must be provided to confirm that the medication is effective, defined as initial response, and recurrence of clinically significant, symptomatic anemia.
Fetal (neonatal) alloimmune thrombocytopenia (FAIT)	- **Initial Authorization:** Up to 2 g/kg per **week** until delivery. - **Continued Authorization:** No reauthorization.
ITP (acute)	- **Initial Authorization:** Up to 2 g/kg total (authorization is for up to 28 weeks). - **Continued Authorization:** No reauthorization (please see ITP [chronic] below for ongoing therapy requests).

Indication [a]	Dosing Schedule
	[a] Hizentra may be authorized up to 0.4 gm/kg/week
ITP (chronic)	- **Initial Authorization:** Up to 2 g/kg per four weeks, up to 28 weeks. - **Continued Authorization:** Up to 2 g/kg per four weeks - Authorization **shall** be reviewed at least every 52 weeks. - **Reauthorization:** Clinical documentation (including, but not limited to chart notes) must be provided to confirm that the medication is effective, with a documented initial response to IVIG and: o Continued thrombocytopenia, defined as a platelet count of < 20,000 OR less than 30,000 cells/m^3 and clinically significant bleeding despite therapy with an alternative chronic therapy. **OR** o Documentation that an alternative chronic therapy has been ineffective, or not tolerated.
ITP in pregnancy	- **Initial Authorization:** Up to 2 g/kg per four weeks, up to delivery. - **Continued Authorization:** No reauthorization (please see criteria for ITP [chronic] for ongoing therapy requests).
Post-transfusion purpura (hemolytic transfusion reaction)	- **Initial Authorization:** Up to 4 g/kg total over up to 4 weeks. - **Continued Authorization:** No reauthorization.
Pure red cell aplasia (PRCA), viral	- **Initial Authorization:** Up to 2 g/kg per four weeks, up to 28 weeks. - **Continued Authorization:** Up to 2 g/kg per four weeks - Authorization **shall** be reviewed at least every 52 weeks. - **Reauthorization:** Clinical documentation (including, but not limited to chart notes) must be provided to confirm that the medication is effective, with documentation of initial response, parvovirus, and recurrence of significant anemia.
Neuroimmunologic disorders	
GBS, Acute inflammatory demyelinating polyneuropathy (AIDP)	- **Initial Authorization:** Up to 2 g/kg per four weeks, up to 12 weeks. - **Continued Authorization:** No reauthorization; please see criteria for Chronic inflammatory demyelinating polyneuropathy (CIDP) for ongoing therapy requests.
Pemphigoid, refractory	- **Initial Authorization:** Up to 2 g/kg per four weeks, up to 26 weeks. - **Continued Authorization:** No reauthorization.
Paraneoplastic opsoclonus ataxia syndrome	- **Initial Authorization:** Up to 2 g/kg per four weeks - Authorization **shall** be reviewed at least every 28 weeks. - **Continued Authorization:** Up to 2 g/kg per 4 weeks. - **Reauthorization:** Clinical documentation (including, but not limited to chart notes) must be provided to confirm that the medication is effective, with documented functional improvement.

Indication [a]	Dosing Schedule
	[a] Hizentra may be authorized up to 0.4 gm/kg/week
Acute demyelinating encephalomyelitis (ADEM) or anti-NMDA receptor encephalitis Chronic inflammatory demyelinating polyneuropathy (CIDP) Lambert-Eaton myasthenic syndrome (LEMS) Multifocal motor neuropathy (MMN) Myasthenia gravis (MG. acute and chronic) Stiff-Person syndrome	- **Initial Authorization:** Up to 2 g/kg per four weeks; up to 28 weeks. - **Continued Authorization:** Up to 2 g/kg per four weeks. - Authorization **shall** be reviewed at least every 52 weeks. - **Reauthorization:** Clinical documentation (including, but not limited to chart notes) must be provided to confirm that the medication is effective, with documented functional improvement.
Dermatomyositis Myositis, including polymyositis and autoimmune myositis Systematic lupus erythematosus (SLE)	- **Initial Authorization:** Up to 2 g/kg per four weeks, up to 28 weeks. - **Continued Authorization:** Up to 2 g/kg per four weeks. - Authorization **shall** be reviewed at least every 52 weeks. - **Reauthorization:** Clinical documentation (including, but not limited to chart notes) must be provided to confirm that the medication is effective, with documented improvement in muscle strength and/or decreased CPK levels.
Transplant (solid organ)	
Prevention of acute rejection (pre- and peri-operative)	- **Initial Authorization:** Up to 2 g/kg per four weeks, up to 12 weeks total. - **Continued Authorization:** No reauthorization. Please see Treatment of antibody (Ab)-mediated (humoral) rejection. -
Treatment of antibody (Ab)-mediated (humoral) rejection	- **Initial Authorization:** Up to 2 g/kg per four weeks, up to 12 weeks total. - **Continued Authorization:** Up to 2 g/kg per four weeks - Authorization **shall** be reviewed after each course (see Reauthorization). - **Reauthorization:** Clinical documentation (including, but not limited to chart notes) must be provided to confirm that one of the following is met: • Persistent rejection: Up to 28 weeks total may be authorized if rejection is persistent, and documentation of a treatment plan has been provided that must include a plan for re-transplantation. • New episode of rejection: Up to 12 weeks total when there is documented improvement from a previous course and confirmation of another episode of rejection.

Indication [a]	Dosing Schedule
	[a] Hizentra may be authorized up to 0.4 gm/kg/week
Other Miscellaneous disorders	
Kawasaki syndrome	- **Initial Authorization:** Up to 4 g/kg total, authorized over an eight-week period. - **Continued Authorization:** No reauthorization
Pediatric intractable epilepsy	- **Initial Authorization:** Up to 2 g/kg per four weeks, up to 28 weeks. - **Continued Authorization:** Up to 2 g/kg per four weeks - Authorization **shall** be reviewed at least every 52 weeks. - **Reauthorization:** Clinical documentation (including, but not limited to chart notes) must be provided to confirm that the medication is effective, with documented significantly reduced frequency and/or duration of seizures.
Post-Exposure prophylaxis against varicella-zoster (VZV)	- **Initial Authorization:** 400 mg/kg as a single dose. - **Continued Authorization:** No reauthorization.
BK Viremia (BK polyomavirus in solid organ transplantation)	- **Initial Authorization:** Up to 2 g/kg total, authorized over a twelve-week period. - **Continued Authorization:** No reauthorization.
PANDAS / PANS	- **Initial Authorization:** Up to 2 g/kg per four weeks, up to 12 weeks (up to 3 months). - **Continued Authorization:** Up to 2 g/kg per four weeks - Authorization **shall** be reviewed at least every 12 weeks (3 months). - **Reauthorization:** Clinical documentation (including, but not limited to chart notes) must be provided to confirm that the medication is effective, with documented significantly reduced severity of symptoms and improvement in functioning. This evaluation must include clinical testing with a validated instrument (see *Appendix 2*), which must be performed pretreatment and posttreatment to demonstrate clinically meaningful improvement.

V. Immune globulin (IVIG/SCIG) is considered investigational when used for all other conditions, including, but not limited to:

1. Acute lymphocytic leukemia
2. Acute renal failure
3. Adrenoleukodystrophy
4. Adult HIV infection
5. Alzheimer's disease
6. Aplastic anemia
7. Asthma
8. Atopic dermatitis
9. Autism
10. Cardiomyopathy, recent-onset dilated
11. Chronic fatigue syndrome
12. Clostridium difficile, recurrent

13. Complex Regional Pain Syndrome (CRPS)
14. Cystic fibrosis
15. Diabetes
16. Diamond-Blackfan anemia
17. Encephalitis, not otherwise specified (in the coverage criteria above)
18. Endotoxemia
19. Heart block, congenital
20. Hemolytic anemia (other than autoimmune)
21. Hemophagocytic syndrome
22. Human T-lymphocyte virus-1 myelopathy
23. Hyper IgE syndrome
24. Immune mediated neutropenia
25. Inclusion body myositis
26. Infectious disease in high-risk neonates and adults following surgery or trauma
27. Lumbosacral plexopathy
28. Narcolepsy/cataplexy
29. Neonatal hemochromatosis
30. Nephropathy, membranous
31. Nephrotic syndrome
32. Neuropathy, not otherwise specified (in the coverage criteria above)
33. Ophthalmopathy, euthyroid
34. Paraproteinemic neuropathy
35. Post-polio syndrome
36. Recurrent spontaneous abortion
37. Rheumatoid arthritis
38. Systemic Sclerosis, diffuse cutaneous (dcSS)
39. Stevens-Johnson Syndrome
40. Still's Disease (Systemic Juvenile Immune Arthritis, SJIA)
41. Surgery or trauma
42. Thrombocytopenia, nonimmune
43. Thrombotic Thrombocytopenic Purpura, including Hemolytic Uremic Syndrome (TTP/HUS), neonatal autoimmune and transfusion refractory.
44. Tic disorder (Based on DSM Criteria)
45. Toxic epidermal necrolysis (TEN)
46. Urticaria, delayed pressure
47. Vasculitic syndromes, other systemic (not specified above), such as antineutrophil cytoplasmic antibody- (ANCA) associated vasculitis [microscopic polyangiitis (MPA)], and eosinophilic granulomatosis with polyangiitis (EGPA) [Churg-Strauss Syndrome (CSS)]
48. Von Willebrand's syndrome

Position Statement

Summary

Intravenous immune globulin (IVIG) [1 2]

- All IVIG preparations are generally considered therapeutically interchangeable.
- Minor immunoglobulin A (IgA) and immunoglobulin G (IgG) subclass differences exist. [32-34]
- IVIG preparations with low IgA content are used to minimize reactions in patients with hypogammaglobulinemia and concurrent IgA deficiency or when anti-IgA antibodies are present in a recipient.
- Differences in formulation may guide product selection (e.g., pre-mixed liquid vs. lyophilized powder, 5% vs. 10%, low sucrose, low osmolarity).
- Given that there are several available IVIG preparations that are generally considered therapeutically interchangeable, the use of significantly more expensive formulations of IVIG are considered not medically necessary and not coverable (i.e., higher-cost immune globulin replacement products as listed in *Table 2*).

Subcutaneous immune globulin (SCIG) [1]

- All immune globulin products for subcutaneous (SC) use are approved for patients with primary immune deficiency (PID). They are available as 16.5% or 20% solutions for weekly SC infusion or as a 10% solution (Hyqvia) for monthly SC infusion.
- Some immune globulin products for intravenous (IV) use may also be for SC administration (see *Tables 1 and 2* above).
- Multiple injection sites (three to eight) are necessary for weekly infusion (all SCIG in *Tables 1 and 2*, excepting Hyqvia) for an average patient because of the volume that must be infused. Hyqvia 10% is formulated with hyaluronidase, to allow for larger volume infusion at a single injection site, dosed monthly.
- SCIG has a lower bioavailability than IVIG, so must be given in higher doses to achieve the same serum IgG concentrations. With exception of Hyqvia, all SCIG formulations require a dose increase versus IVIG.
- However, SC delivery may result in higher steady-state IgG levels due to less variation in IgG levels.
- Most of these products have not been approved for SC administration for any indication, other than PID. Because other diagnoses usually require larger doses (based on grams per kilogram) with a high volume per dose, SC administration is generally not feasible. Therefore, use of SCIG in excess of the doses listed in the Quantity Limits (*Tables 1 and 2*) is considered "not medically necessary." Higher doses of immune globulin replacement therapy may be given with intravenous (IVIG) products.
- Injection site swelling, redness, and itching were reported in the majority of patients.
- Given that there are several available SCIG preparations that are generally considered therapeutically interchangeable, the use of significantly more expensive formulations of SCIG are considered not medically necessary and not coverable.

Dosing Considerations and Therapeutic Levels for Replacement Therapy for Treatment of Immunodeficiency with Hypogammaglobulinemia [3]

- Dosing adjustment in replacement therapy is based on clinical response and IgG levels.
    * The trough or steady state IgG level is obtained before scheduled infusions and frequently guides immune globulin replacement therapy (IVIG/SCIG) dose selection.
    * The minimum serum concentration of IgG necessary for protection has not been firmly established. However, maintenance of serum trough IgG levels above 500 mg/dL has been considered a sufficient target to prevent most systemic infections. Some patients may require a higher IgG level for protection.
- Immune globulin replacement therapy is a blood product and by nature, in limited supply and costly to prepare and administer. Long toxicity associated with immune globulin replacement (IVIG/SCIG) therapy includes potential risk of renal toxicity and thrombotic events. As such, use of immune globulin replacement therapy should be limited to specific conditions with proven benefit, when diagnostic criteria are met, and used by, or in consultation with, appropriate subspecialists.
- Dosing of immune globulin replacement therapy for conditions other than hypogammaglobulinemia do NOT require monitoring of IgG levels. Efficacy in conditions other than hypogammaglobulinemia is based on clinical response, including improvement or resolution of disease symptoms, up to the maximum covered dose (per the Quantity Limits above).

Clinical Efficacy

IMMUNODEFICIENCY (Primary or Secondary) - Replacement Therapy for Hypogammaglobulinemia

Primary humoral immunodeficiency diseases [1 3 4]

- All available immune globulin replacement products are FDA-approved for use in primary immunodeficiency (PID).
- X-linked agammaglobulinemia (congenital agammaglobulinemia) occurs in male infants, usually presenting in the first 3 years of life.
- Common variable immunodeficiency (CVID; acquired hypogammaglobulinemia; adult onset hypogammaglobulinemia; dysgammaglobulinemia) is characterized by low to normal IgG levels and inability to produce an antibody response to protein (e.g., tetanus) or carbohydrate antigens (e.g., Pneumovax). Most patients experience severe recurrent and/or chronic infections.
- Combined immunodeficiency syndromes, including Wiskott-Aldrich syndrome, are rare, inherited syndromes.
- Immunoglobulin reference ranges vary depending on the age of the patient and the particular assay method used. The usual immune globulin maintenance dose is 100-800mg/kg/month and therapy is usually life-long.

- Hypogammaglobulinemia in neonates [5]
    * Treatment with IVIG is usually reserved for patients with recurrent severe infections, not responding to antibiotic prophylaxis.
    * The usual IVIG dose is 400 – 600 mg/kg/month, administered as a single dose, or up to several months in duration.

Acquired Deficiencies:

- Hematologic malignancy-related hypogammaglobulinemia (including B-cell cancers, multiple myeloma, and post-bone marrow transplant (BMT). [6 7]
    * Use of immune globulin replacement in hypogammaglobulinemia patients with B-cell cancers (including CLL), multiple myeloma and post-allogeneic bone marrow transplant (BMT) is supported by guidelines.
    * IVIG therapy reduces the incidence of bacterial infections in patients with hematologic malignancies and secondary hypogammaglobulinemia.
    * Previously, use of IVIG prophylaxis post-BMT was common for prevention of graft versus host disease (GVHD); however, with improved immunosuppressant regimens, the use of routine IVIG prophylaxis is no longer supported.
    * Monthly IVIG infusions of 400 mg/kg are recommended to maintain the serum IgG level.
- HIV-infected children < 13 years of age[8]
    * Current guidelines recommend IVIG use among HIV-infected children who have hypogammaglobulinemia (IgG <400 mg/dL), to prevent serious bacterial infections (SBIs).
    * IVIG is no longer recommended for primary prevention of SBIs in children, unless hypogammaglobulinemia is present. During the pre-HAART (highly-active antiretroviral therapy) era, IVIG was shown to decrease the frequency of bacterial infections and hospitalization in children with AIDS, however only in those not receiving daily Pneumocystis carinii pneumoniae (PCP) prophylaxis.

AUTOIMMUNE (IMMUNE-MEDIATED) DISORDERS

- Pooled immune globulin (IVIG) has been studied and found to be useful in a variety of autoimmune disorders, including hematologic, neuromuscular and infectious disease-related diseases. However, given the rarity of many of these disorders, the evidence for safety and efficacy in some diagnoses is insufficient at this time.
- The mechanism of action of IVIG in autoimmune disorders is thought to include acute neutralization of circulating autoantibodies, toxins, and cytokine modulation, as well as long-term reduction of antibody production and suppression of T-cell cytokines.

Hematologic (immune-mediated) Disorders: [6]

Acquired Factor VIII inhibitor [9-14]

- A sufficient treatment course is usually 6-12 weeks before attempting a different immunosuppressive agent. Patients are generally treated until remission (elimination of the inhibitor) occurs, which may take several months.

- Treatment regimens of 1 gm/kg for 2 days or 400 mg/kg for 5 days have been studied. In one study, only 6 of 19 patients responded to IVIG within 40 days of treatment.

Fetal (neonatal) alloimmune thrombocytopenia (FAIT): [15 16]

- ACOG guidelines recommend IVIG as first line treatment for documented fetal thrombocytopenia.
- A trial comparing IVIG treatment with and without dexamethasone in siblings showed that:
  * IVIG treatment was associated with an increase in mean platelet count of 69,000/mm^3.
  * There were no instances of intracranial hemorrhages, although hemorrhage had occurred previously in 10 untreated siblings.
- The recommended dose of IVIG is 1 gm/kg/week, increasing to 2 gm/kg/week in refractory cases.

Idiopathic thrombocytopenia purpura (ITP) [6 17-20]

- Normal platelet count range is 115,000/mm^3 to 440,000/mm^3.
- Acute ITP
  * Acute ITP is usually seen in children and typically resolves spontaneously within 2 months.
  * Approach to management of children with observation, steroids, and/or IVIG is based on severity and type of bleeding (such as mucosal versus non-mucosal).
  * In various studies, a majority of IVIG recipients attained platelet counts greater than 100,000 cells/mm^3 within 7 days.
  * A maximum of 1 gm/kg/day for three or four doses of IVIG on alternate days is recommended.
- Chronic ITP
  * Current evidence does not support that IVIG alters the natural course of chronic ITP, affects long-term morbidity/mortality, or increases the rate of long-term remission.
  * IVIG is not indicated for the maintenance of platelet counts in chronic ITP; however, IVIG maybe be used episodically in patients with chronic ITP, for acutely low platelet levels.
  * Steroids are considered the first-line treatment of choice for chronic ITP. Although the use of IVIG may be considered as a steroid-sparing adjunctive therapy for chronic ITP, other therapies with a more durable response should be considered, such as splenectomy, rituximab, Promacta (eltrombopag) or Nplate (romiplostim).
  * IVIG may be considered in patients with dangerously low platelet counts (less than 10,000 to 20,000 per mm^3 in adults or less than 30,000 per mm^3 in children) or patients undergoing an invasive procedure, and therefore may be at an increased risk for significant bleeding, such as intracranial hemorrhage.

    * Choosing Wisely, an evidence-based initiative to promote wise use of medical resources, states that patients with ITP should not be treated in the absence of bleeding or a very low platelet count. Only rarely should patients be treated when platelet counts are above 30,000, such a preparation of surgery or an invasive procedure. Unnecessary treatment exposes patients to potential adverse events and raises the overall cost of care, with unknown clinical benefit. [20]
    * The usual dose of IVIG is 1 to 2 gm/kg divided into equal amounts and given over 2 to 5 days.

- ITP in pregnancy (a.k.a. Pregnancy-Associated ITP) [6 15 19]
    * The goal of therapy is to minimize the risk of bleeding complications due to thrombocytopenia.
    * Platelet function is typically normal, so it is not necessary to maintain platelet count in the normal range.
    * The first line of treatment is prednisone, usual dose 1-2 mg/kg/day.
    * IVIG is useful in cases that are resistant to steroids and when a rapid rise in platelets is necessary. A response typically occurs within 6 – 72 hours of IVIG treatment.
    * For patients nearing the end of their pregnancy and preparing for use of epidural anesthesia, IVIG coverage will be considered under "ITP, acute" criteria, for use prior to an invasive procedure. Because the evidence is less useful in determining the exact threshold platelet levels needed for prevention of bleeding, the use of IVIG is generally at the discretion of the treating anesthesiologist or surgeon, and pregnant patients are managed like non-pregnant patients.
    * The American College of Obstetrics and Gynecology (ACOG) recognizes the high cost of IVIG therapy and suggests consultation from a physician experienced in the treatment of ITP when considering use of IVIG therapy.
        ▪ Guidelines recommend that, except for the delivery, treatment indications for pregnant women are similar to those currently recommended for any patient.
        ▪ At the time of delivery, management of ITP is based on an assessment of maternal bleeding risks associated with delivery, epidural anesthesia, and the minimum platelet counts recommended to undergo these procedures (80 X 10^9/L for epidural placement and 50 X 10^9/L for cesarean delivery)

<u>Post-transfusion purpura</u> (hemolytic transfusion reaction) [19 21]

- Post-transfusion purpura is a rare condition that can occur in patients undergoing blood transfusions. It typically develops approximately one-week after blood transfusion.
- IVIG may be considered first-line therapy in severely affected patients.
- The recommended dose of IVIG is 500 mg/kg/day for two consecutive days. Rapid platelet recovery has been seen within days of treatment.

Pure Red Cell Aplasia (PRCA), Viral [19 22]

- Parvovirus B19 infects and lyses red cell precursors, which can cause pure red cell aplasia. IVIG therapy is usually reserved for patients with chronic parvovirus infection and chronic anemia.
- Chronic parvovirus infection with anemia usually occurs in immunocompromised patients. If the immunodeficiency improves, the parvovirus and anemia may spontaneously resolve.
- The usual dose of IVIG is 2-4 grams/kg, divided as 400 mg/kg/day for 5 – 10 days, 1 gm/kg/day for 3 days or 0.5 gm/kg weekly for 4 weeks. Initial treatment courses may be indicated with recurrence of anemia and increase in parvovirus B19 DNA.

Neuromuscular Disorders:

Inflammatory demyelinating polyneuropathy (IDP) [23-28]

- Guillain-Barré syndrome (GBS) and Acute IDP[22,23, 90][23-25]
    * Diagnostic criteria for GBS include all of the following:
        - Progressive weakness of the extremities, the trunk, bulbar and facial muscles, and external ophthalmoplegia.
        - Reduction or absence of deep tendon reflexes in weak limbs.
        - Presence of demyelination on electrodiagnostic studies may be present but is not required for the diagnosis of GBS.
    * IVIG appears to be effective in adult patients with Guillain-Barré syndrome when given within 2 weeks of symptom onset.
    * The recommended IVIG dose is 400 mg/kg/day for 5 days. If relapse occurs within 1-2 weeks of initial therapy, an additional treatment course of IVIG may be effective. Further treatment does not improve outcomes and is not recommended.
- Chronic IDP (CIDP)[26-28]
    * Clinical guidelines recognize the use of specific diagnostic criteria for CIDP, to exclude other causes of neuropathy and confirm the presence of peripheral nerve demyelination.
        - Objective criteria include use of electrodiagnostic (EMG) testing, along with additional studies, such as nerve biopsy or lumbar puncture (LP) to confirm elevation of CSF protein.
        - Given the lack of consensus across guidelines and need to exclude neuropathies unlikely to respond to IVIG therapy, use of objective criteria are required to support a clinical diagnosis of CIDP.
    * Treatment options include plasmapheresis, IVIG, and corticosteroids.
    * The usual IVIG dose is 400 mg/kg/day for 5 days, repeated every 6 weeks.

Autoimmune encephalitis: acute demyelinating encephalomyelitis (ADEM) or anti-NMDA receptor encephalitis

- Immune-mediated encephalitis is relatively rare and include ADEM and encephalitis syndromes associated with antibodies against neuronal tissue, such as anti-NMDA receptor encephalitis.

- The differential diagnoses list for autoimmune encephalitis is extensive and may include diagnoses considered investigational in this policy. Therefore, IVIG is considered not coverable, until the diagnosis is clarified.

Acute demyelinating encephalomyelitis (ADEM) [29]

- ADEM can be associated with various neurologic and psychiatric symptoms, including cognitive and speech dysfunction, seizures, dyskinesias, altered consciousness, and autonomic instability.
- High-dose IV corticosteroid therapy is considered the first-line treatment for ADEM, with IVIG or plasma exchange reserved for patients not responding to steroid therapy.
- The usual IVIG dose is 400 mg/kg/day for 5 days.

Anti-NMDA receptor encephalitis (anti-NMDAR)[29 30]

- Anti-NMDA receptor encephalitis is a specific type of autoimmune encephalitis, diagnosed by detection of IgG antibodies against a subunit of NMDA receptors in serum or CSF. It can be associated with various neurologic and psychiatric symptoms, including cognitive and speech dysfunction, seizures, dyskinesias, altered consciousness, and autonomic instability.
- The diagnosis of anti-NMDAR is confirmed by very specific testing, IgG antibodies to the GluN1 (also known as NR1) subunit of the NMDA receptor in CSF. However, given access to testing and delays in results, available standard diagnostic tests can support the diagnosis, including CSF, EEG, and brain MRI.
- Based on large case series and years of experience in clinical practice, use of immunosuppression therapy is the standard of care, with corticosteroids, IVIG, plasma exchange, cyclophosphamide, or rituximab. IVIG (400 mg/kg/day for 5 days) in combination with high-dose methylprednisolone or plasma exchange may be useful in treating patients with anti-NMDA receptor encephalitis in the first-line setting. Rituximab and/or cyclophosphamide may be of benefit in patients not responding to IVIG and steroids within 10 days. Children are generally managed with monotherapy (cyclophosphamide or rituximab).

Dermatomyositis (DM), adult and pediatric (juvenile)[26 31-34]

- High-dose IVIG is a safe and effective treatment for refractory dermatomyositis unresponsive to corticosteroid therapy. [26 31 32]
- For adults, abnormalities on EMG or elevations in CPK are accepted diagnostic criteria.
- Juvenile dermatomyositis (JDM) is characterized by a vasculopathy affecting both the muscle and the skin. For pediatric patients, a number of muscle enzymes, including CPK, LDH, AST or aldolase, may be used to confirm the diagnosis. Myositis may also be confirmed by an abnormal muscle biopsy, EMG or MRI. Children can also have specific skin manifestations associated with the dermatomyositis, including Gottron papules on the dorsal surface of the knuckles and heliotrope rash over the eyelids.[33]
- The recommended IVIG dose is 2 gm/kg per month.

Lambert-Eaton myasthenic syndrome (LEMS)[26 31 35]

- LEMS is a rare acquired autoimmune disorder characterized by proximal weakness of extremities, decreased reflexes, and dryness of mouth and eyes.
- IVIG improved limb, respiratory muscle, and bulbar muscle strength in a small, randomized trials. [34]
- The recommended dose of IVIG is 2 gm/kg administered over 2 – 5 days.

Multifocal motor neuropathy (MMN) [31 36-43]

- MMN is a progressive neuropathy with asymmetric, distal weakness of at least one limb, upper extremities more frequently than lower extremities.
- Small, controlled trials demonstrate significant increase in muscle strength associated with IVIG administration, long-term benefits, and safety (44 patients across four small trials of IVIG induction therapy as compared to placebo). [36-40]
- The recommended IVIG dose is 2 gm/kg/month, administered over 2 – 5 days.[31 42]
- Additionally, patients with anti-GM1 antibodies show an increased chance of response to IVIG. However, anti-GM antibodies are present in only 30-80% of patients with MMN and are not specific to MMN. In addition, patients who lack anti-GM1 antibodies may have a favorable response to IVIG; therefore, the clinical utility of monitoring anti-GM1 antibodies is uncertain. [41]

Myasthenia gravis (MG) [26 44 45]

- IVIG may be useful in treating patients with severe myasthenia gravis acutely, or as maintenance therapy for patients who fail to respond to the maximum tolerated doses of corticosteroids and/or immunosuppressants.
- Randomized trials examining short-term treatment of myasthenia gravis with IVIG have shown no difference between IVIG and plasma exchange or IVIG and methylprednisolone.
- There is no evidence to determine whether IVIG improves function or reduces steroid requirements for moderate to severe myasthenia gravis.
- The recommended dose of IVIG is 1 – 2 gm/kg/month administered over 2 – 5 days.

Opsoclonus-myoclonus ataxia (OMA)

- Opsoclonus-myoclonus ataxia (OMA) is a rare neurological syndrome characterized by an unsteady gait, brief shock-like muscle spasms, and irregular rapid eye movements and can be a paraneoplastic (e.g., with neuroblastoma) or non-paraneoplastic syndrome.
- Evidence supporting the use of IVIG for OMA consists mainly of retrospective chart reviews and case reports in children and adults. [46]
- However, one randomized phase 3 placebo-controlled trial for the use of IVIG for children with opsoclonus-myoclonus associated with neuroblastomas found a reduction in OMA in the IVIG-treated group as compared to placebo (81 versus 41%). All patients received steroids and chemotherapy. IVIG was dosed 1 gm/kg on days 0 and 1 of each 28-day cycle.[48]

Pemphigoid bullous (e.g., pemphigus foliaceus, pemphigus vulgaris) [34 49]

- IVIG is typically given in refractory disease, in combination with conventional treatments, such as immunosuppressive agents and plasmapheresis, and is discontinued once conventional treatment (such as corticosteroids, azathioprine, cyclophosphamide, etc.) takes effect. IVIG is not considered a maintenance therapy for pemphigus foliaceus, pemphigus vulgaris or other autoimmune mucocutaneous blistering diseases.
- The usual dose of IVIG is 1-2 gm/kg administered over 3 days. This regimen may be repeated every 3-4 weeks.

Polymyositis 24, 25, 32[26 31 32]

- Polymyositis is an inflammatory myopathy with no unique clinical features. It is typically a diagnosis of exclusion in patients with slowly progressive muscle weakness.
- Traditional therapies include immunosuppressive medications or steroids.
- IVIG may be considered for patients not responding to first-line immunosuppression.
- The recommended dose of IVIG is 2 gm/kg/month administered over 2 – 5 days.

Stiff Person Syndrome 24, 44 [26 50]

- Sixteen patients were randomized to IVIG or placebo for 3 months, and then crossed over to the alternate treatment after a 1-month washout period. IVIG patients demonstrated decreased stiffness scores, decreased frequency of falls, ability to walk more easily without assistance, and improved ability to perform work-related tasks. Benefits lasted 6 weeks to 1 year without additional treatment.
- The usual dose of IVIG is 400 mg/kg/day for 3 – 5 days.

Systemic Lupus Erythematosus

- Small case series suggest some benefit from treatment with IVIG when compared to cyclophosphamide.
- The usual dose of IVIG is 400 mg/kg/day for 5 days.

Transplant (Solid Organ):

Antibody-mediated rejection (AMR) 45-47 [51-53]

- Acute allograft (organ) rejection may be cellular (T-cell mediated) or humoral (antibody-mediated) (AHR, AMR).
- The standard for diagnosis of rejection is a transplant biopsy. [52]
- Pre-treatment with IVIG (desensitization) may reduce the risk of AMR in “highly sensitized” renal and/or heart transplant patients, also referred to as “with donor specific antibodies (DSAs” [52 53]
- A randomized, double-blind trial comparing IVIG to placebo in 101 highly sensitized renal transplant candidates concluded that IVIG is better than placebo in improving transplantation rates. [51]
- Acute humoral rejection (AHR) is also an AMR and can occur outside of the peri-operative period, but most commonly within 6 months after transplant. The diagnosis is confirmed by a renal biopsy. The goal of therapy is early antibody elimination with IVIG, pheresis, or a combination of modalities.

- A variety of protocols have been developed for the use of IVIG in treating AMR after solid organ transplant. [52 53]

Other Miscellaneous Disorders:

Kawasaki syndrome][54 55]

- IVIG in conjunction with aspirin given within the first 10 days of illness can reduce the incidence of coronary artery abnormalities, compared with treatment with aspirin alone. IVIG is not effective if more than ten days have elapsed from onset of symptoms.
- The usual dose of IVIG is 2 gm/kg as a single dose but may be repeated if the patient fails to defervesce.

BK viremia (BK polyomavirus in solid organ transplantation) [56-59]

- The American Society of Transplantation Infectious Diseases Community of Practice (AST-IDCOP) recommends a stepwise reduction of immunosuppressive therapy until serum BK levels are no longer detectable. Although there are no randomized controlled trials, this approach is supported by a meta-analysis and a number of large prospective observational studies reporting successful clearance BK virus in 80% to 100% of cases.
- Reduction of immunosuppressants is often done in a stepwise fashion:
    * Immunosuppressants for solid organ transplants include calcineurin inhibitors (such as cyclosporine and tacrolimus), antimetabolites (such as azathioprine and mycophenolate), and steroids (prednisone).
    * Immunosuppression reduction may begin with a reduction of either the calcineurin inhibitor or antimetabolite by 50%, eventually leading to a discontinuation of the antimetabolite.
- The highest IVIG dose studied in BK viremia was 2g/kg, given over several days to weeks. The optimum dose, frequency, and duration for IVIG use in BK viremia varies greatly and needs further evaluation. However, there is no evidence to support higher, longer, or repeated doses of IVIG.
- Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS) / Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) [60-64]
    * PANDAS/PANS are syndromes with an abrupt onset of symptoms and associated temporally with a Group A beta-hemolytic streptococcal infection. The symptoms generally are abnormal behavioral (neurologic and psychiatric in nature) and may include obsessive-compulsive disorder (OCD), tic disorders (verbal or motor), and cognitive issues. Other symptoms may include emotional symptoms (e.g., anxiety, emotional lability, irritability, aggression, oppositional behaviors), reduced performance in school (related to deficits in attention and memory, hyperactivity, and cognitive changes), sensory or motor abnormalities, and somatic symptoms (sleep disturbance, enuresis, or urinary frequency). [64]
    * A recent consensus statement from the PANS Research Consortium indicates that IVIG has been used in clinical practice for PANS/PANDAS; however, this statement also acknowledged the lack of high-quality evidence in this area. [60 62]
    * There is currently insufficient evidence that IVIG is more effective than any other approach for treatment of for PANS/ PANDAS. Case series and case

reports, as well as initial low-quality studies in small numbers of subjects, have suggested that IVIG may be efficacious in PANS/PANDAS. However, good quality, randomized, double-blinded trials have failed to show any significant difference between IVIG and placebo during the blinded study period. [61 63] Any recommendation for treatment is based on very low-quality evidence, including expert opinion and lower-quality observational data. [64]

* Of note, there is a lack of consensus among experts that PANDAS is an autoimmune disorder. As such, use of immunomodulators is not universally recommended and some experts caution against their use. [63]

* Because the safety and efficacy of IVIG remains inconclusive, the use of IVIG is coverable for PANS/PANDAS only when: [64]
  - PANS/PANDAS is diagnosed by a subspecialist (such as a pediatric neurologist, pediatric psychiatrist, neurodevelopmental pediatrician, pediatric rheumatologist, pediatric allergist/immunologist) and
  - IVIG use is endorsed by the primary care provider (such as a family physician or pediatrician) and
  - An appropriate clinical trial of less intensive treatments is ineffective for sustained reduction in symptoms. Less intensive treatments investigated for management of PANDAS/PANS include antimicrobials, anti-inflammatories, and psychoactive therapies:
    * Antimicrobials: short-course antibiotic therapy for confirmed Group A beta-hemolytic strep infection (14-day course, minimum).
    * Anti-inflammatory therapies: initial therapy with nonsteroidal anti-inflammatory drugs (NSAIDs) for 5-7 days. Corticosteroids may be used if suboptimal response to NSAIDs (sufficient course).
    * Psychoactive therapies: selective serotonin reuptake inhibitors (SSRIs) and/or behavioral therapy [such as cognitive behavioral therapy (CBT), or
    * Given lack of clearly recommended specific treatments by guidelines among a large variety of available of less intensive treatment options available, IVIG is coverable only when <u>at least</u> two of these listed above are ineffective, as detailed in the coverage criteria.
    * Plasma exchange (PLEX), tonsillectomy, and adenoidectomy are also treatment options in this setting, which are not required but may be considered valid prior step therapies.
  - A baseline evaluation is completed and includes detailed documentation of neuropsychiatric symptoms and associated functional impairment. Clinical testing with a validated instrument must be performed pretreatment and posttreatment to demonstrate clinically meaningful improvement (see *Appendix 2*). Use of non-validated instruments are not sufficient (see *Appendix 3*).

INVESTIGATIONAL CONDITIONS

- The University Hospital Consortium (UHC), an alliance of 68 academic health centers, performed a critical assessment of off-label IVIG uses.
- The UHC determined published data to be inadequate to support the use of IVIG in various conditions. [65]
- Asthma: Further trials in asthma patients are necessary to delineate patient subsets that would best benefit from IVIG therapy and define optimal dosing in this condition. [66-69]
- HIV (adults): The use of IVIG in HIV-infected adults is not definitive to substantiate a positive benefit on overall long-term health outcomes. [70]
- Multiple sclerosis, progressive: There is not substantial evidence to support IVIG in the treatment of chronic progressive multiple sclerosis. [71 72]
- Multiple sclerosis; relapsing-remitting type (RRMS): IVIG may provide some benefit in reducing the acute exacerbation rate in relapsing-remitting multiple sclerosis.[73]
    * Trials are generally limited to small numbers of patients and have lacked complete data on clinical outcomes.
    * Current evidence suggests little benefit with regard to slowing disease progression.
    * The American Academy of Neurology does not consider IVIG to be a first-line therapy in the treatment of relapsing-remitting multiple sclerosis. Instead, disease modifying therapies (DMTs) should be initiated (see *Medications for Multiple Sclerosis Policy* in *Cross Reference*s for more information).
- Neuropathy, other (not listed in the criteria): Other neuropathies, such as small fiber neuropathy and autonomic autoimmune neuropathy NOS
    * The differential diagnoses list for neuropathy is extensive and may include diagnoses considered investigational in this policy.
    * Therefore, IVIG is not coverable until the diagnosis is clarified, for evaluation versus coverage criteria.
    * *Specific to small fiber neuropathy*: The available literature for the use of IVIG for small fiber neuropathy is limited to case reports/case series,[74] along with two small double-blind, placebo-controlled trials in patients with small fiber neuropathy (SFN), one with painful idiopathic small fiber neuropathy (I-SFN)[75] and a more recent trial with SFN associated with two autoantibodies, trisulfated heparin disaccharide (TS-HDS) and fibroblast growth factor receptor 3 (FGFR-3). [76]
        - Available case reports/ case series reported inconsistent and transient results. [74]
        - The trial in idiopathic SFN reported no significant effect on pain in patients with painful I-SFN with use of IVIG. It would require 10 patients to be treated for a single person to have a 1-point change in an 11-point pain scale. Disease modification effect was not measured. [75]

- The trial in SFN and autoantibodies to TS-HDS and FGFR-3 did not find a benefit with use of IVIG versus placebo.[76]
- Therefore, given that lack of meaningful benefit, the use of IVIG for small fiber neuropathy is considered investigational and not coverable.
- The underlying cause needs to be treated (such as sarcoid, diabetes, Sjogren).
- Pain treatment options include antidepressants [tricyclics (TCAs), serotonergic norepinephrine reuptake inhibitors (SNRIs)], anticonvulsants, corticosteroids, topical pain cream, analgesics, and tramadol.

* *Specific to autoimmune neuropathy* (a.k.a. immune-mediated neuropathy): [77-79]
  - The diagnosis of autoimmune neuropathy, including autoimmune autonomic neuropathy, requires exclusion of other immune-mediated neuropathy causes, such as Guillain-Barre Syndrome (GBS), demyelinating polyneuropathy, and multifocal motor neuropathy (MMN).
  - For autoimmune neuropathy associated with systemic autoimmune disease (such as vasculitis, rheumatoid arthritis, lupus, Sjogren syndrome), the underlying cause needs to be treated.
  - The available literature for the use of IVIG for autoimmune autonomic neuropathy is limited to case reports/case series and one recent small RCT in chronic residual peripheral neuropathy in microscopic polyangiitis (no clear benefit of IVIG).[79] Other reported treatment options include mycophenolate, prednisone, azathioprine, and rituximab alone or in combination. Additional evidence is needed to establish the benefit of IVIG.
* *Paraproteinemic neuropathy:* neuropathies associated with a monoclonal gammopathy or paraprotein, including IgG or IgA paraproteinemic neuropathy. Insufficient evidence is available to establish benefit from IVIG. [80]

- Optic neuritis (ON): There is insufficient evidence for the use of IVIG for optic neuritis.[81 82]
  * Optic neuritis is characterized by acute monocular visual loss. Demyelinating optic neuritis is a frequent condition in patients with a diagnosis of multiple sclerosis. Optic neuropathies due to other conditions are numerous and addressed elsewhere.
  * The use of IVIG for optic neuritis is not supported by available evidence. One small RCT (n=32) failed to demonstrate a statistically significant benefit in improvement of the primary endpoint of logarithm of the minimum angle of resolution (logMAR), a measure of visual acuity as compared to IV methylprednisolone ("steroid pulse") for steroid-resistant ON.[81]
  * At this time, the standard of care treatment for steroid-resistant ON in patients with abnormal brain MRIs is initiation of disease-modifying therapies (DMTs) for clinically isolated syndromes (CIS) suggestive of MS.

- Post-Polio: Trials of IVIG for post-polio syndrome failed to demonstrate a statistically significant benefit in improvement of muscle strength. [83]
- Recurrent pregnancy loss, or recurrent spontaneous abortion (due to anti-phospholipid or anti-cardiolipin antibodies): [84-87]
    * Recurrent pregnancy loss is defined as three or more pregnancies resulting in spontaneous abortion prior to 20 weeks of gestational age. These women often have immunologic abnormalities, particularly antiphospholipid antibodies.
    * IVIG has not been established as a safe or effective therapy to prevent recurrent spontaneous abortion in women with immunologic abnormalities, such as elevated natural killer cells, defective cytokines, or defective growth factors. [84]
    * One randomized controlled trial comparing IVIG to thyroid replacement therapy for the prevention of miscarriages found IVIG to be less effective. There was a statistically significant higher rate of live birth among women treated with thyroid replacement therapy. [85]
    * A small randomized controlled trial in 85 women with a history of three or more spontaneous abortions before 10 weeks of gestation compared low molecular heparin (LMW) plus aspirin with IVIG therapy. The percentage of live births in the LMW plus aspirin versus the IVIG treatment group was 72.5% and 39.5%, respectively. [86]
    * A randomized controlled trial in 82 women with a history of idiopathic secondary miscarriage compared live birth rates in those who received IVIG versus placebo infusion (saline). There was no statistical difference between treatment groups. [[84]
    * ACOG recommendations state:[87]
        - If results are positive for the same antibody on two consecutive tests 6 to 8 weeks apart, initiate heparin and low-dose aspirin with next pregnancy attempt.
        - IVIG is not effective in preventing recurrent pregnancy loss.
- Additional conditions for which published data is determined to be inconclusive or inadequate to support the use of IVIG include Alzheimer's disease, atopic dermatitis, recurrent *C. difficile*, complex regional pain syndrome (CRPS), narcolepsy/cataplexy, neonatal hemochromatosis, chronic sinusitis, tic disorder, delayed pressure urticaria, systemic sclerosis (diffuse cutaneous, dcSS) and toxic epidermal necrolysis[88-98]

Appendix 1: Primary Humoral Immunodeficiencies, as defined by the following diagnostic criteria:
1. X-linked agammaglobulinemia (congenital agammaglobulinemia) diagnosis accompanied by marked deficits or absence of all five immunoglobulin classes (IgG, IgM, IgA, IgE, and IgD), decreased circulating B lymphocytes, and normal numbers of functioning T lymphocytes. **OR** **2.** Hypogammaglobulinemia (a general term describing serum levels of IgG which are below the lower limits of normal). **OR** **3.** Common variable immunodeficiency (CVID; acquired hypogammaglobulinemia; adult onset hypogammaglobulinemia; dysgammaglobulinemia) documented with low to normal IgG levels and the inability to produce an antibody response to protein (e.g., tetanus) or carbohydrate antigens (e.g., Pneumovax). **OR** **4.** Immunoglobulin subclass deficiency (e.g., X-Linked immunodeficiency with hyper-IgM) accompanied by very low serum concentrations of IgG, IgA, and IgE, with normal or, more frequently, greatly elevated polyclonal IgM concentrations. **OR** **5.** Combined immunodeficiency syndromes, including Wiskott-Aldrich syndrome, accompanied by marked deficits in IgG, IgA and IgM, low lymphocyte counts, and absent or below normal levels of both B- and T-lymphocytes.

Appendix 2: Validated Neuropsychological Tests for PANS/PANDAS[64]	
Assessment of:	**Validated Test**
Motor and vocal tics, obsession and compulsion	• Children's Yale–Brown Obsessive Compulsive Scale (CY- BOCS) for presence and severity of motor and vocal tics • Yale Global Tic Severity Scale (YGTSS) for presence and severity of child's obsession and compulsion
Anxiety	Multidimensional Anxiety Scale for Children (MASC) for the presence and types of child's anxiety symptoms for ages 8 to 19 years.
Short-term memory and attention	• Digit Span subtest Wechsler Intelligence Scale for Children for verbal short-term memory for ages 6 to 16 years • Coding subtest Wechsler Intelligence Scale for Children for visual-motor dexterity and nonverbal short-term memory for ages 6 to 16 years; and • Symbol Search subtest Wechsler Intelligence Scale for Children for accuracy, attention and concentration for ages 6 to 16 years.
Processing speed	Processing Speed Index Wechsler Intelligence Scale for Children (WISC III-IV) for speed of cognitive processes and response output on visual-motor tasks for ages 6 to 16 years
General	Global Impairment Score scale to measure impairment in children and adolescents

Appendix 3: Other Neuropsychological Tests (non-validated) [64]	
Assessment of:	**Test**
General	• Achenbach System of Empirically Based Assessment (ASEBA),19 Mini international neuropsychiatric interview (M.I.N.I.- KID) or equivalent - general assessment of psychiatric conditions • Child and Adolescent Trauma Screen (CATS) for trauma screening • Children's Global Assessment Scale (C- GAS) for general functioning • Clinical Global Impression- Severity Scale (CGI- S) for severity of the patient's illness at time of assessment • Pediatric Quality of Life Inventory (PedsQL) for quality of life • Work and Social Adjustment Scale (WSAS) 2 for impaired functioning • KIDSCREEN for subjective health and well- being
Anxiety	The Screen for Child Anxiety Related Disorders (SCARED)
Executive Function	Behavior Rating Inventory of Executive Function (BRIEF)
Screening for psychiatric diagnoses	Kiddie Schedule for Affective Disorders and Schizophrenia (Kiddie- SADS)
Inattention, hyperactivity and impulsivity	ADHD rating scale (ADHD- RS)

Cross References
BlueCross BlueShield Association Medical Policy, 8.01.05 - Immunoglobulin Therapy. [November 2022]
Medications for thrombocytopenia, Medication Policy Manual, Policy No. dru648
Medications for multiple sclerosis, Medication Policy Manual, Policy No. dru753
Products with Therapeutically Equivalent Biosimilars/Reference Products, Medication Policy Manual, Policy No. dru620
Site of Care Review, Medication Policy Manual, Policy No. dru408

Codes	Number	Description (Injection, immune globulin)
HCPCS	J1459	Injection, immune globulin (Privigen), intravenous, non-lyophilized (e.g., liquid), 500 mg
HCPCS	J1460	Injection, gamma globulin, intramuscular, 1 cc
HCPCS	J1554	Injection, immune globulin (Asceniv), 500 mg
HCPCS	J1555	Injection, immune globulin (Cuvitru), 100 mg
HCPCS	J1556	Injection, immune globulin (Bivigam), 500 mg
HCPCS	J1557	Injection, immune globulin, (Gammaplex), intravenous, non-lyophilized (e.g., liquid), 500 mg
HCPCS	J1559	Injection, immune globulin (Hizentra), 100 mg
HCPCS	J1561	Injection, immune globulin, (Gamunex-C/Gammaked), non-lyophilized (e.g., liquid), 500 mg
HCPCS	J1566	Injection, immune globulin, intravenous, lyophilized (e.g., powder), not otherwise specified, 500 mg
HCPCS	J1568	Injection, immune globulin, (Octagam), intravenous, non-lyophilized (e.g., liquid), 500 mg
HCPCS	J1569	Injection, immune globulin, (Gammagard liquid), non-lyophilized, (e.g., liquid), 500 mg
HCPCS	J1572	Injection, immune globulin, (Flebogamma/Flebogamma Dif), intravenous, non-lyophilized (e.g., liquid), 500 mg
HCPCS	J1576	Immune globulin intravenous, human - ifas (Panzyga)
HCPCS	J1575	Injection, immune globulin/hyaluronidase, (HYQVIA), 100 mg immune globulin
HCPCS	J1599	Injection, immune globulin, intravenous, non-lyophilized (e.g., liquid), not otherwise specified, 500 mg

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Revision History

Revision Date	Revision Summary
9/19/2024	Effective 1/1/2025, moved Hyqvia from Table 2 ('Not Medically Necessary' Higher-Cost Immune Globulin Replacement Products) to Table 1 (Coverable Immune Globulin Replacement Products).
6/20/2024	New IVIG product, Alyglo (immune globulin intravenous, human-stwk), added to policy as medically necessary.
3/21/2024	Effective 3/21/2024: • Clarification of the following criteria: - Multifocal motor neuropathy (MMN) diagnostic criteria, for operational consistency. - Myasthenia gravis (MG) step therapy criteria, to align with other medication policies for MG for administrative consistency (no change to intent of coverage criterion). - PANDAS/PANS step therapy criteria (from three to two step-therapies), as required by Oregon State DFR 11/14/2023 Notice of Coverage Requirement). • Correction of the products considered not medically necessary in the Continuation of Therapy (COT) criteria. Changed criteria I. to refer to the products listed in *Table 2*. • Removed Carimune from the policy (no longer commercially available). • Renamed *Table 2* to specify "High-Cost". • Corrected coverable dose in *Table 1* and *Table 2* to match Dosing Schedule in *Table 3*.
9/14/2023	Effective 1/1/2024: • Added coverage criteria for PANDAS/PANS. • Clarified "diagnosis by, or in consultation with" subspecialist throughout the diagnostic criteria. No change to intent of criteria. • Moved following products to "not medically necessary," for both Continuation of therapy (COT) and New Starts: - IVIG: Bivigam, Gammaplex, Panzyga - SCIG: Cuvitru, Hyqvia
3/16/2023	Clarified Guillain-Barré syndrome (GBS) criteria to include, but not be limited to acute inflammatory demyelinating polyneuropathy (AIDP).
6/17/2022	Moved Asceniv to "not medically necessary," for both Continuation of therapy (COT) and New Starts.
4/21/2021	• Coverage criteria and quantity limit for use in BK viremia added. • Continuation of therapy (COT) language updated (no change to intent).

Revision Date	Revision Summary
10/28/2020	• Clarified policy quantity limits and intent. • Added coverage for postexposure VZV prophylaxis.
4/22/2020	Added continuation of therapy (COT) criteria (no change to intent of coverage criteria).
7/24/2019	• Add Asceniv (IVIG), Xembify (SCIG) and Cutaquig (SCIG) to policy (new products) • Clarified coverage criteria for ADEM and anti-NMDA receptor encephalitis are specific to those two specific diagnoses. ADEM and anti-NMDA receptor encephalitis are types of autoimmune encephalitis. Autoimmune encephalitis (not otherwise specified) is considered a non-specific diagnosis and is not coverable. • Broadened coverage criteria for: - ITP of pregnancy (align platelet count to guidelines; 20,000) - LEMS (remove step therapy) • Investigational Uses: - Added PANDAS/PANS - Removed Behçet's syndrome, Neonatal hemolytic disease, Multiple Sclerosis, Uveitis and Wegener's granulomatosis. • Clarified Quantity Limits (QL): - Added QL per dose (and month) for SCIG and IVIG products. - Modified QL for treatment of immune-mediated rejection to allow up to six months if re-transplant is the treatment plan. • Update HCPCS Codes.
8/17/2018	• Added Panzyga to policy. • Added investigational use: Complex Regional Pain Syndrome • Updates HCPCS Codes
1/18/2018	Add Gammaked to policy.
4/14/2017	• Clarify coverage criteria for CIDP • Add coverage criteria for refractory acute demyelinating encephalomyelitis (ADEM) and anti-NMDA encephalitis • Clarify re-authorization period for Immunodeficiency (Replacement Therapy)
11/11/2016	Removed site of care language from the individual drug policy; however, requirements still apply. Reference to *Site of Care Review*, dru408 is provided as part of criterion IA.
9/15/2016	Add Cuvitru to policy.

Revision Date	Revision Summary
4/8/2016	• Reworded coverage criteria for Polymyositis to Refractory Myositis. Move Dermatomyositis (juvenile) criteria, to follow after Refractory Myositis. • Delete requirement for IgG levels for reauthorization for hypogammaglobulinemia in re-authorization table (typographical error).

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Medication Policy Manual

Policy No: dru029

Topic: Synagis, palivizumab, Respiratory syncytial virus (RSV) immune prophylaxis

Date of Origin: January 1997

Committee Approval Date: June 20, 2024

Next Review Date: 2025

Effective Date: November 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Synagis (palivizumab) is an antibody used in the prevention of respiratory syncytial virus (RSV) which may cause lower respiratory tract disease in certain high-risk infants and children younger than 24 months.

Policy/Criteria

Most contracts require pre-authorization approval of Synagis (palivizumab) prior to coverage.

I. Continuation of therapy (COT): Synagis (palivizumab) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, full policy criteria must be met for coverage.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Synagis (palivizumab) may be considered medically necessary for children when there is clinical documentation (including, but not limited to chart notes) that criteria A. **AND** B. are met:

A. **Beyfortus** (nirsevimab-alip) is unavailable due to manufacturer shortage, use is contraindicated, or prior therapy was not tolerated.

AND

B. One of the following criteria (1. through 6.) below is met:

1. Chronic lung disease (CLD) of prematurity [also known as bronchopulmonary dysplasia (BPD)]: Infants or children with CLD of prematurity when criteria a, b, and c below are met.

a. Gestational age less than 32 $^{0/7}$ weeks.

AND

b. A requirement for greater than 21% oxygen for at least 28 days after birth).

AND

c. Chronological age <u>at the start of the current RSV season</u>, as defined by criterion 1. or 2. below:

1. Less than or equal to 12 months chronological age.

OR

2. Greater than 12 months but less than or equal to 24 months chronological age for children who continue to require medical intervention (supplemental oxygen, chronic corticosteroids, or diuretic therapy) during the 6-month period before the start of the second RSV season.

PLEASE NOTE: In the absence of ongoing medical intervention for CLD (medications or oxygen), Synagis (palivizumab) is NOT coverable for children age 12-24 months

OR

2. <u>Congenital heart disease (CHD)</u>: Infants or children with hemodynamically significant congenital heart disease who are less than or equal to 12 months chronological age at the start of the current RSV season when criterion (a., b., or c.) is met.

a. Receive medication to control congestive heart failure or will receive medication as a result of a planned cardiac surgery.

OR

b. Have moderate to severe pulmonary hypertension.

OR

c. Have cyanotic heart disease.

PLEASE NOTE: The use of Synagis (palivizumab) is considered <u>not</u> medically necessary for children with CHD greater than 12 months chronological age at the start of the current RSV season.

OR

3. Infants less than or equal to 12 months chronological age with neuromuscular disease or congenital abnormality that impairs the ability to clear secretions from the upper airway because of ineffective cough.

OR

4. <u>Estimated gestational age less than 29 weeks</u>: Infants less than or equal to 12 months chronological age (post-natal age) at the onset of the current RSV season and born before 29 $^{0/7}$ weeks gestation.

OR

5. Immunocompromised: Infants or children less than 24 months chronological age who will be profoundly immunocompromised during the current RSV season due to one of the following criteria (a. through d.) below.

a. Solid organ transplant.

OR

b. Hematopoietic stem cell transplant.

OR

c. Chemotherapy.

OR

d. Immunocompromised due to other conditions with either lower respiratory tract symptoms (including use of ongoing supplemental oxygen therapy), lymphopenia, or corticosteroid therapy.

OR

6. Cystic fibrosis: Infants or children with cystic fibrosis when criterion a. or b. below is met for the chronological ages indicated at the start of the current RSV season.

a. Less than or equal to 12 months chronological age with clinical evidence of chronic lung disease and/or nutritional compromise.

OR

b. Greater than 12 months but less than or equal to 24 months chronological age when 1 or more of the following are present:

1. Manifestations of severe lung disease (previous hospitalization for pulmonary exacerbation in the first year of life or chest imaging abnormalities that persist when stable).
2. Weight for length less than the 10th percentile.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Synagis (palivizumab) coverable only under the medical benefit (as a provider-administered medication).

B. When a member meets the applicable criteria above, coverage is authorized annually during the local RSV season.

C. When a member meets the applicable criteria above, Synagis (palivizumab) will be authorized in quantities of up to 5 doses, up to 15 mg/kg, for monthly dosing until the end of the current RSV season.

IV. RSV immunoprophylaxis with Synagis (palivizumab) is considered not medically necessary for any of the following:

A. Infants who do not meet the criteria above.

B. Infants and children with hemodynamically insignificant heart disease, such as mild cardiomyopathy not requiring medical therapy, secundum atrial septal defect, small ventricular septal defect, pulmonic stenosis, uncomplicated aortic stenosis, mild coarctation of the aorta, and patent ductus arteriosus.

C. Infants with lesions adequately corrected by surgery unless they continue to require medication for congestive heart failure (and criteria IB. above is met).

D. Patients with cystic fibrosis who do not meet the criteria above.

E. Patients with Prader-Willi Syndrome (PWS) who do not meet the criteria above.

F. Patients with recurrent wheeze who do not meet the criteria above.

G. Patients with Down syndrome who do not meet the criteria above.

V. Synagis (palivizumab) is considered investigational when used for any other indication, including:

A. RSV immunoprophylaxis in adults.

B. Treatment of RSV infections (in children or adults).

C. Use after Beyfortus (nirsevimab-alip) in the same RSV season.

Position Statement

Summary

- Synagis (palivizumab) has not been shown to be safer or more effective than other immunoprophylaxis options to prevent complications of respiratory syncytial virus (RSV) infection in infants and children who are at high risk of severe RSV disease, such as Beyfortus (nirsevimab-alip). However, use of Synagis (palivizumab) is significantly more costly. Therefore, Synagis (palivizumab) is only coverable when Beyfortus (nirsevimab-alip) is unavailable or use is contraindicated, and the "high-risk" criteria are met [for specific children who have risk factors or other underlying medical conditions that would predispose them to significant respiratory complications due to RSV infection].
- Synagis (palivizumab) has only been proven to decrease the chance of being hospitalized from RSV in some pediatric patients who are at high risk of severe RSV disease. [1,2] The evidence to support the efficacy of Synagis (palivizumab) is limited and unreliable, and the benefit of RSV immunoprophylaxis with Synagis (palivizumab) may be modest.
- Synagis (palivizumab) has not been shown to prevent mortality from RSV infection.
- This medical policy is consistent with the American Academy of Pediatrics (AAP) Red Book update (February 21, 2024) and the Centers for Disease Control and Prevention (CDC) which recommends Beyfortus (nirsevimab-alip) over Synagis (palivizumab).[3,4]

- When Beyfortus (nirsevimab-alip) is not available or contraindicated, Synagis (palivizumab) is recommended in high-risk infants as outlined in the AAP Redbook (2021) "2021-2024 Report of the Committee on Infectious Disease" and associated guidance issued in 2014. [2-6]).
- There is no evidence to support the use of Synagis (palivizumab) after the use of Beyfortus (nirsevimab-alip). Therefore, the use of Synagis (palivizumab) after the use of Beyfortus (nirsevimab-alip) immunoprophylaxis is considered investigational.

Clinical Efficacy

- Clinical trials have demonstrated efficacy for Synagis (palivizumab) in reducing hospitalization due to RSV infection, and reductions in other measures of severity of RSV infection. [7]
- Impact RSV Study [Synagis (palivizumab) versus placebo] [7]
    * The Impact RSV Study reported a 55% reduction in RSV-related hospitalizations ($p < 0.001$). RSV hospitalization was 4.8% in the Synagis (palivizumab) group compared to 10.6% in the placebo group (number needed to treat = 17).
    * Among secondary endpoints, the incidence of intensive care unit (ICU) admission during hospitalization for RSV infection was lower among patients receiving Synagis (palivizumab) than among those receiving placebo (1.3% and 3.0%, respectively), but there was no difference in the mean duration of ICU care between the two groups.
    * A cohort study showed that Synagis (palivizumab) administered to infants born at 32 to 35 weeks estimated gestational age did not result in direct cost savings related to hospitalization or ambulatory care. [8]
- In the Synagis (palivizumab) CHD Study, Synagis (palivizumab) reduced RSV hospitalizations by 45% ($p < 0.003$) which correlates to a number needed to treat of 23. [9]
- In a double-blind, randomized, placebo-controlled trial of 429 otherwise healthy preterm infants with recurrent wheeze, Synagis (palivizumab) treatment resulted in a relative reduction in the total number of wheezing days during the first year of life. However, Synagis (palivizumab) is considered not medically necessary for this condition as there is no clear correlation to decreased wheezing days and effect on health outcomes. [10]

National Guidelines

<u>American Academy of Pediatrics (AAP)</u> [2-6]

- The AAP and the Advisory Committee on Immunization Practices (ACIP) recommends the use of Beyfortus (nirsevimab-alip) over Synagis (palivizumab) for RSV immunoprophylaxis unless Beyfortus (nirsevimab-alip) is unavailable or contraindicated to administer. However, Synagis (palivizumab) should continue to only be used in high-risk infants as outlined in the Red Book (2021).
- The AAP recognizes the high cost-to-benefit ratio for RSV immunoprophylaxis with Synagis (palivizumab). Therefore, guidelines define the pediatric populations that best benefit from RSV immunoprophylaxis.

- The AAP provides recommendations for RSV immunoprophylaxis in children who have risk factors or other underlying medical conditions that would predispose them to respiratory complications due to RSV infection.
- The AAP guidance also includes detailed lists of the types of patients not at increased risk of RSV infection and therefore should not receive RSV immunoprophylaxis.
- The AAP recommends that parents can reduce the risk of an RSV infection by practicing good handwashing, washing blankets and toys regularly, limiting exposure to environmental pollutants, not smoking around their children, and avoiding crowds during RSV season.
- Regarding exposure to indoor air pollutants, the AAP recommends that infants at high risk for RSV infection should never be exposed to tobacco smoke.
- Breastfeeding should be encouraged for all infants; however, lack of breastfeeding is not a defined risk for RSV. Therefore, RSV immunoprophylaxis is not specifically recommended for infants unable to breastfeed.
- Determination of RSV season: see *Dosing* section below.

Rationale for Changes to National Guidelines

- Guidance for the recommended use of Synagis (palivizumab) was issued in July 2014 and re-affirmed in the most recent Red Book (2021). Significant changes from previous recommendations include the following: [2,5,6]
    - Synagis (palivizumab) is no longer recommended for otherwise healthy infants born at or after 29 $^{0/7}$ weeks. The AAP continues to recommend avoidance of crowds and group childcare during the RSV season for high-risk infants.
        - A study performed by the New Vaccine Surveillance Network (NVSN), sponsored by the Centers for Disease Control and Prevention (CDC) found that some previously reported potential risk factors (e.g., siblings in the household, child-care attendance) were not associated with a significantly increased risk of RSV hospitalization.
        - This same study also found that the RSV hospitalization rate for preterm infants was not significantly different from the rate for term infants (4.6/1000 and 5.3/1000, respectively); although, infants born at less than 30 weeks' gestation had a higher risk of RSV hospitalization than did infants born at 30 to 33 weeks gestation.
        - Additional cohort studies in various states and varying groups of preterm infants also support that the greatest increase in risk of RSV hospitalization is in preterm infants born before 29 weeks gestation.
    - Synagis (palivizumab) is no longer recommended in the second year of life except for some children with chronic lung disease and cystic fibrosis, and for some profoundly immunocompromised children.
    - In a prospective population-based surveillance study of 5,067 children younger than five years, 75% of those hospitalized were younger than 12 months.
        - There is limited safety data and no efficacy data to support the use of Synagis (palivizumab) in the second year of life, RSV hospitalization rates

decline for all children with the second season, regardless of the presence or absence of comorbidities.

* The definition of chronic lung disease and the associated recommendations have been clarified.
* Guidance for use of Synagis (palivizumab) in some infants with hemodynamically significant CHD, immunocompromised children and some children with cystic fibrosis has been provided.

Hemodynamically Significant CHD

- Certain children who are 12 months or younger with hemodynamically significant CHD may benefit from palivizumab prophylaxis. Children with hemodynamically significant CHD who are most likely to benefit from immunoprophylaxis include infants with acyanotic heart disease who are receiving medication to control congestive heart failure and will require cardiac surgical procedures and infants with moderate to severe pulmonary hypertension.

Immunocompromised

- RSV infection in immunocompromised children and adults can progress to respiratory failure and death. In several retrospective analyses of RSV-infected individuals, the majority of deaths that occurred were in those with lower respiratory tract disease. Profound lymphopenia (< 100 cells/mm^3) was associated with progression to lower respiratory tract disease, and, therefore, is a risk factor for poor outcomes due to RSV infection.
- Other risk factors for poor outcomes due to RSV infection include chronological age younger than two years, lower respiratory tract symptoms at presentation, and corticosteroid therapy.

Cystic fibrosis

- While routine use of Synagis (palivizumab) is not recommended in children with cystic fibrosis, it may be considered when other conditions (e.g., chronic lung disease, nutritional compromise) are present.
- Two recent reviews of RSV infection in infants with cystic fibrosis concluded that they may be at a slightly higher risk of hospitalization; however, there is insufficient data to support a universal recommendation for this group.

- When Synagis (palivizumab) is recommended, it may be given for up to 5 monthly doses for qualifying children (see *Dosing* below).

Safety

- Hypersensitivity reactions have been reported on initial exposure or re-exposure to Synagis (palivizumab). [1]
- Rare cases of anaphylaxis (< 1 case per 100,000 patients) have been reported following re-exposure to Synagis (palivizumab). [1]

Dosing

- RSV immunoprophylaxis is initiated at the onset of the annual RSV season and terminated at the end of RSV season.[2]
    * Determination of RSV season: Season onset can be determined in real time by identifying the first week of 2 consecutive weeks that RSV RT-PCR test positivity is 3% or greater or antigen detection positivity is 10% or greater. [2]
        - Per the National Respiratory and Enteric Virus Surveillance System (NREVSS) in 2013, the onset week in an area (national, regional, or state) is defined as the first of 2 consecutive weeks when the weekly mean of the percentages of specimens testing positive for RSV antigen in all reporting laboratories in the area is ≥ 10%. [12]
        - However, since 2014, most laboratories replaced RSV antigen tests with PCR testing (RSV RT-TR). [13]
        - Reporting by individual state and county health departments may vary. Either test result can be used for the purposes of this coverage policy.
    * The offset is the last of 2 consecutive weeks when the mean percent positive drops below this threshold. The season duration is the onset week, the weeks between onset and offset, and the offset week. The peak is the week when the mean percentage of positive RSV antigen tests is the highest. [12]
    * In most areas of the United States, with the exception of Alaska and Florida, the usual time for the beginning of the RSV season is October to December, and termination is March to early April. [2]
    * Regional differences account for a later RSV season experienced in the Pacific Northwest, which is typically from November through April. [11]
    * The onset of the RSV season is variable in different regions of Florida. Despite this variation, a maximum of 5 doses of palivizumab is recommended to provide 6 months of protective serum concentrations of palivizumab. Use of Florida Department of Health data may be helpful to determine start date of palivizumab prophylaxis.
    * Alaska Native populations in southwest Alaska experience a higher risk of hospitalization due to RSV and have a longer RSV season. Given the differences in epidemiology of RSV and the cost of emergency air transportation out of remote locations, eligibility for palivizumab prophylaxis may differ from infants in the continental United States. Use of RSV surveillance data from the state of Alaska may be helpful to determine start and stop date of palivizumab prophylaxis.
    * Data from the past year's surveillance season is used as a predictor for the timing of the next year's outbreak. This information is updated annually. For current RSV trends, refer to: http://www.cdc.gov/surveillance/nrevss/rsv/index.html.
- The recommended treatment course for Synagis (palivizumab) from the prescribing information is up to 5 total doses. Doses should be administered every 30 days starting in early November. [2]

- The AAP confirms the recommendation of a maximum of 5 total doses with the following statement: [5,6]

  > "Results from clinical trials indicate that palivizumab trough serum concentrations more than 30 days after the fifth dose will be well above the protective concentration for most infants. Five monthly doses of palivizumab will provide more than 20 weeks of protective serum antibody concentration. In the continental United States, a total of five monthly doses for infants and young children with congenital heart disease, CLD, or preterm birth before 32 weeks gestation (31 weeks, 6 days and younger) will provide an optimal balance of benefit and cost, even with variation in season onset and end.
  >
  > Children who qualify for palivizumab prophylaxis for the entire RSV season should receive palivizumab only during the 5 months following the onset of RSV season in their region (maximum of 5 doses), which should provide coverage during the peak of the season, when prophylaxis is most effective."

- The AAP Red Book (2021-2024) reaffirms the position in the 2014 guidance: [2]

  > "Because 5 monthly doses of palivizumab at 15 mg/kg/dose will provide more than 6 months of serum palivizumab concentration above the desired serum concentration for most infants, administration of more than 5 monthly doses is not recommended within the continental United States. Children who qualify for palivizumab prophylaxis should receive the first dose at the onset of the RSV season. For qualifying infants born during the RSV season, fewer than 5 doses will be needed to provide protection until the RSV season ends in their region (maximum of 5 doses).
  >
  > A small number of sporadic RSV hospitalizations will occur before or after the main season in many areas of the United States, but the greatest benefit from prophylaxis is derived during the peak of the season and not when the incidence of RSV hospitalization is low."

- Although Synagis (palivizumab) is NOT coverable in infants and children with stable congenital heart disease (CHD), operationally, Synagis (palivizumab) criterion B.1. "Receive medication to control congestive heart failure" would be met on the day of a planned surgery. Therefore, this criterion would be considered "met" two weeks prior to the planned surgical date, to allow for adequate prophylaxis lead-time. However, Synagis (palivizumab) criteria would be met for coverage only if the other criteria are met for CHD, namely age less than or equal to 12 months.

Cross References
BlueCross BlueShield Association Medical Policy, 5.01.10 - Immune Prophylaxis for Respiratory Syncytial Virus. [September 2022]

Codes	Number	Description
CPT	90378	Respiratory Syncytial Virus Immune Globulin (RSV-IgM), IM Use, 50 mg

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Revision History

Revision Date	Revision Summary
6/20/2024	• Added step criteria through Beyfortus (nirsevimab-alip). • Added sequential use of Synagis after Beyfortus to the list of Investigational Uses.
6/15/2023	No changes with this annual update.
6/17/2022	Added clarification in "Chronic lung disease" and "Immunocompromised due to other conditions" criteria.
7/16/2021	Added clarification in congenital heart disease.
7/22/2020	Added COT language. No other criteria changes with this annual update.
7/24/2019	No changes with this annual update.
7/23/2018	No changes with this annual update.
8/11/2017	No changes with this annual update.
8/12/2016	No changes with this annual update.

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Medication Policy Manual | **Policy No:** dru048

Topic: Myobloc, rimabotulinumtoxinB | **Date of Origin:** December 14, 2001

Committee Approval Date: December 7, 2023 | **Next Review Date:** December 2024

Effective Date: March 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Botulinum toxin is a neurotoxin that is injected into a muscle to cause temporary paralysis or relaxation of that muscle. This policy covers the one commercial botulinum toxin type B product, Myobloc (rimabotulinumtoxinB). Botulinum toxin type A products (Botox, Dysport, and Xeomin) are covered in a separate policy.

Please note: Botulinum toxin for use in gender affirming care is covered in a separate policy, Gender-Affirming Care Products, dru757

Policy/Criteria

Most contracts require pre-authorization approval of Myobloc (rimabotulinumtoxinB) prior to coverage.

I. Continuation of therapy (COT): Myobloc (rimabotulinumtoxinB) may be considered medically necessary for COT when criterion A, B, or C below are met.

A. For potentially cosmetic indications, including **hyperhidrosis**, full policy criteria below must be met for coverage.

OR

B. For all other indications, criteria 1 and 2 below must be met:

1. The patients was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Myobloc (rimabotulinumtoxinB) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) showing that criterion A, B, or C is met.

A. **Cervical dystonia** or **spasmodic torticollis,** when criteria 1 and 2 below are met:

1. Documentation of involuntary contractions of the neck muscles resulting in twisting and repetitive movements, and/or abnormal postures.

AND

2. Documented pain or functional impairment originating from the dystonia.

OR

B. **Sialorrhea** (drooling), excessive.

OR

C. **Urinary incontinence** due to detrusor overactivity [idiopathic or neurogenic causes (e.g. due to spinal cord injury, multiple sclerosis), or overactive bladder (OAB)], when therapy with anticholinergic agents or Myrbetriq (mirabegron) is ineffective or not tolerated.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Myobloc (rimabotulinumtoxinB) coverable only under the medical benefit (as a provider-administered medication).

B. **Initial Authorization:** When pre-authorization is approved, Myobloc (rimabotulinumtoxinB) may be authorized in quantities up to 4 injection treatments within a 48-week period.

C. **Continued Authorization:**

1. Authorization may be reviewed at least every 12 months. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

2. Additional treatments may be authorized on a case-by-case basis if documentation of objective measures supporting the need for more frequent dosing are provided.

IV. Myobloc (rimabotulinumtoxinB) is considered investigational for all other conditions, including, but not limited to:

A. Carpal tunnel syndrome.

B. Hyperhidrosis (such as axillary or palmar).

C. Spasticity not otherwise specified (other than spasmodic torticollis), such as:

1. Cerebral palsy (CP)-related spasticity.

2. Hemifacial spasm.

3. Spasmodic dysphonia.

4. Spasmodic dystonia.

5. Spastic movement disorders in children.

6. Spastic trismus, including TMJ.

7. Upper limb spasticity following stroke.

Position Statement

Summary

- Myobloc (rimabotulinumtoxinB) is a form of botulinum toxin type B and is approved for the treatment of cervical dystonia or spasmodic torticollis to reduce the severity and pain associated with abnormal neck position.
- Myobloc (rimabotulinumtoxinB) is also used for reduction of sialorrhea in patients with a variety of neurological disorders. The goal of therapy is to reduce sialorrhea-associated complications, such as aspiration pneumonia or skin breakdown. For urinary incontinence due to detrusor overactivity, Myobloc (rimabotulinumtoxinB) may be a treatment option for patients with symptoms not responding to other treatment options.

- The intent of this policy is to allow coverage for specific diagnoses where there is demonstrated safety and efficacy from clinical trials to support their use, including spasmodic conditions, and other specific indications.
- Botulinum toxins (BTX-A and BTX-B) have also been studied in many different conditions where muscle tension is thought to play a role. The quality of evidence from the majority of these studies is poor.
- FDA labeling indicates that units of Myobloc (rimabotulinumtoxinB) cannot be compared to or converted into units of any other botulinum toxin. [24] Therefore, the efficacy, dosing and safety of Myobloc (rimabotulinumtoxinB) cannot be based on extrapolation from other studies using other botulinum toxin serotypes.
- Use of botulinum toxin (all serotypes) for treatment of wrinkles or other cosmetic conditions is considered not medically necessary and frequently excluded by contract.

Clinical Efficacy

Cervical Dystonia or Spasmodic Torticollis

- Cervical dystonia (or spasmodic torticollis) is characterized by involuntary contractions of the neck muscles resulting in twisting and repetitive movements, and/or abnormal postures.
- Results from three clinical studies support the efficacy of rimabotulinumtoxinB in reducing neck pain and the severity of the abnormal head position associated with cervical dystonia or spasmodic torticollis in patients previously responsive to BTX-A [1,2] or those patients who no longer respond to BTX-A. [3]

Sialorrhea

- Anatomically guided injections of Myobloc (rimabotulinumtoxinB) into the parotid and submandibular glands appear to effectively improve sialorrhea in patients with Parkinson's disease. [4-6] and amyotrophic lateral sclerosis (ALS). [7]
- A randomized controlled trial demonstrated a decrease in frequency and severity of sialorrhea in children with cerebral palsy who received rimabotulinumtoxinB injected into the salivary glands. [8]

Urinary Incontinence due to overactive bladder (OAB)

- Injection of Myobloc (rimabotulinumtoxinB) into the bladder appears to improve urinary urgency, frequency and nocturia in patients with refractory detrusor overactivity.
- A Cochrane review concluded both botulinum type A and B formulations are effective treatment options for urinary incontinence due to refractory detrusor overactivity due to neurogenic or idiopathic OAB. [9]

Use of botulinum toxic type B in other conditions

- The evidence for the use of Myobloc (rimabotulinumtoxinB) in a variety of conditions is limited to pilot trials and case reports, including hyperhidrosis (axillary and palmar), [10-13] carpal tunnel syndrome, [14] and myofascial pain due to nerve entrapment (e.g. piriformis syndrome or shoulder impingement). [15,16] The evidence from these trials is of poor quality and the response to therapy was variable. Larger, well-designed trials are necessary to confirm the results, as well as establish benefit relative to standard of care treatments.

- Similarly, small pilot studies, case reports and observational studies have suggested potential benefit of Myobloc (rimabotulinumtoxinB) in the treatment of various spastic disorders (other than spasmodic torticollis), including spasmodic dystonia, [17] upper limb spasticity following stroke, [18,19] spastic movement disorders in children, [20] arm dystonia in children with cerebral palsy, [21] spastic trismus a muscle spasm of the jaw, which may include the temporomandibular joint (TMJ), [22] and hemifacial spasm. [23] The evidence from these trials is of poor quality. Larger, well-designed clinical trials are needed to assess safety and efficacy of rimabotulinumtoxinB in these conditions.

Safety [24]

- The most commonly reported adverse events observed in clinical trials of Myobloc (rimabotulinumtoxinB) include dry mouth, dysphagia, dyspepsia, and injection site pain.
- All botulinum toxin products have a boxed warning and Risk Evaluation and Mitigation Strategy (REMS) program for the potential for toxin to spread from the site of injection and produce symptoms consistent with botulinum toxin effects. Symptoms may include asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence and breathing difficulties and may occur hours to weeks after injection. Swallowing and breathing difficulties can be life threatening. Deaths have been reported.
- The safety, efficacy and dosage of botulinum toxins have not been established for any condition in children less than 12 years of age.

Cross References
BlueCross BlueShield Association Medical Policy, 5.01.05 - Label Use of Botulinum Toxin. [November 2023]
BlueCross BlueShield Association Medical Policy, 8.01.19 - Treatment of Hyperhidrosis. [July 2023]
Surgical Treatments for Hyperhidrosis, Medical Policy; Med 165.
Botulinum toxin type A injection, Medication Policy Manual, Policy No. dru006
Cosmetic and Reconstructive Surgery, Surgery Section; Medical Policy No. 12.
Gender-Affirming Care Products, Medication Policy Manual, Policy No. dru757

Codes	**Number**	**Description**
HCPCS	J0587	Injection, rimabotulinumtoxinB (Myobloc), 100 units

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Revision History

Revision Date	Revision Summary
12/7/2023	No criteria changes with this annual review.
12/9/2022	Added Myrbetriq (mirabegron) as an acceptable step for Urinary incontinence, due to detrusor overactivity [such as overactive bladder (OAB)]. No change to intent.
1/20/2021	• Revised continuation of therapy (COT) criteria. • Reworded urinary incontinence criteria to align with botulinum toxin A policy. • Clarified initial and continued authorization periods. Clarified that more frequent doses may be covered on a case-by-case basis.
1/22/2020	Added COT criteria (no change to intent of coverage criteria).
1/31/2019	• No coverage criteria changes with this annual update. • Clarified documentation language (No change to intent).
1/19/2018	No coverage criteria changes with this annual update
2/17/2017	• Clarified quantity limits to 4 doses per 48-weeks (versus use of 12 months). • Clarified authorization "may" be reviewed every 12 months.
2/12/2016	No criteria changes.
12/14/2001	New policy.

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Medication Policy Manual | **Policy No:** dru135

Topic: Compounded Medications | **Date of Origin:** July 28, 2006

Committee Approval Date: December 9, 2022 | **Next Review Date:** December 2023

Effective Date: March 1, 2023

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

The FDA defines drug compounding as the process by which a pharmacist or doctor combines, mixes, or alters ingredients to create a medication tailored to an individual patient's needs.

In order to be covered, a compounded prescription medication must contain at least one federal legend drug in therapeutic amounts. A federal legend drug is defined as a medication product that by Federal law bears the statement "Caution – Federal (U.S.A.) law prohibits dispensing without a prescription" or words of similar meaning (such as "Rx only"). Bulk chemicals, medical food supplements and nutritional additives not approved for dispensing by prescription are not considered federal legend drugs. The policy below defines criteria that must be met in order for compounded prescriptions to be covered.

PLEASE NOTE: If a compounded medication contains only ingredients that are excluded under the member's benefit (including, but not limited to, bulk chemicals and OTC products), it will be excluded from coverage regardless of the criteria below.

Policy/Criteria

I. Continuation of therapy (COT): Compounded medications may be considered medically necessary for COT when all criteria A, B, and C below are met.

A. The patient is established on this therapy AND one of the following situations apply (criterion 1 or 2 below):

1. Prior to current health plan membership AND the medication was covered by another health plan.

OR

2. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission AND there is documented clinical benefit.

AND

B. The active ingredient in the compounded prescription medication contains at least one federal legend drug component.

AND

C. If a compounded prescription medication is similar to a commercially available product, but differs from the commercially available product in dosage, dosage form, and/or omission of dye, sweetener, flavoring, or preservative, then clinical documentation is required from the prescriber supporting the clinical need for compounded medication.

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. A compounded prescription medication may be considered medically necessary when criteria A through D below are met:

A. The active ingredient in the compounded prescription medication contains at least one federal legend drug component.

AND

B. The active ingredient is present in therapeutic amounts, based on scientific literature or national compendia.

AND

C. The safety and effectiveness for the compounded medication and its route of administration (including the delivery system) is supported by scientific literature or national compendia.

AND

D. If a compounded prescription medication is similar to a commercially available product, but differs from the commercially available product in dosage, dosage form, and/or omission of dye, sweetener, flavoring, or preservative, then clinical documentation is required from the prescriber supporting the clinical need for the compounded medication.

III. Authorization may be reviewed annually to confirm that current medical necessity criteria are met and that the medication is effective.

IV. Drug compounding for the sole purpose of convenience is considered not medically necessary.

Position Statement

Summary

- The FDA recognizes the ability of pharmacists or physicians to engage in traditional extemporaneous drug compounding of reasonable quantities of drugs in response to receipt of a valid prescription. [1]
- Drug compounding may be required to fit the medical needs of a patient because a medication is not commercially available in the necessary strength or dosage form. Drug compounding may also be required for:
    * Preparation of a medication that has been withdrawn from the market for economic concerns, NOT safety.
    * Patients who require liquid formulations or rectal suppositories due to difficulty or inability to swallow.
    * Allergies to dyes, preservatives, or fillers in commercial products which require allergy-free medications.
- When the sole purpose of drug compounding is for the sake of convenience to the physician, other health care provider, and/or the patient, the compounded drug is not considered medically necessary.

Federal and State Regulation

- The FDA provides rules and guidance to assure compounding activities performed by pharmacies and/or physician offices are maintained within the realm of traditional pharmacy practice and that activities are not those that would be considered manufacturing and distributing of an unapproved new drug. [1,2]
- The FDA receives guidance from the Pharmacy Compounding Advisory Committee (PCAC), which was established to advise the FDA on scientific, technical, and medical issues related to drug compounding. The FDA will also consult with the PCAC before issuing certain regulations. [2,3]
- Regulation of compounding is generally done at the state level. States may vary in their regulation and definitions of compounding. The FDA has oversight when compounding is considered manufacturing.

Compounded Pellets (implants) – such as naltrexone or testosterone

- There is significant interest in the use of various medications given as pellets (or implants). Commercially available implants include, but are not limited to: [4]
    * Testosterone pellet (available commercially as generic testosterone pellet, or brand Testopel 75 mg)
    * Buprenorphine implant (available commercially as Probuphine)
    * Various contraceptive implants

- However, the use of compounded pellets (or implants) are not coverable, per the coverage criteria. The rationale is as follows:
    * Most compounded pellets (or implants) are made with a bulk powder or chemical and do NOT contain a "federal legend drug," as defined in the coverage criteria. Any compound that does not contain a federal legend drug is contractually excluded from coverage.
    * In addition, like many other compounds, there is insufficient evidence to establish the safety or efficacy of compounded pellets (or implants), the pellet dosage form, nor the amount of active ingredient in the pellet (including its pharmacokinetics).
- Naltrexone subcutaneous (SC) implant:
    * Naltrexone is available as FDA-approved long-acting injectable suspension (Vivitrol), as well as orally as a 50 mg scored tablet. [4]
    * The safety and efficacy of the compounded product (naltrexone SC implant pellet), the pellet dosage form, nor the amount of naltrexone in this dosage form (including its pharmacokinetics) is not well established. While it may be similar to other compounded products studied, consistent dose and release profiles are not supported by the current literature.
- Testosterone compounded pellet:
    * Testosterone is available as an FDA-approved long-acting pellet (Testopel, as 75 mg pellets), as well as several other topical, injectable, and oral dosage forms. [4]
    * The safety and efficacy of compounded testosterone products (including testosterone pellet other than Testopel and any strength other than 75 mg), the pellet dosage form, nor the amount of testosterone in this dosage form (including its pharmacokinetics) is not well established.

Cross References
Extended-release (ER) Opioid Medication Products for Pain, Medication Policy Manual, Policy No. 515
Immediate-release (IR) Opioid Medication Products for Pain, Medication Policy Manual, Policy No. 516
Testosterone replacement therapy products, Medication Policy Manual, Policy No. 548

References

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3. Federal Food and Drug Administration. Pharmacy Compounding Advisory Committee Roster. https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PharmacyCompoundingAdvisoryCommittee/ucm381301.htm (accessed March 16, 2015).
4. Facts & Comparisons 4.0 (electronic version, updated periodically), Wolters Kluwer Health, Inc.

Revision History

Revision Date	Revision Summary
12/9/2022	Removed criterion 2E, requiring medical necessity review for any compounded ingredient that requires pre-authorization. This is done to streamline operational efficiencies with our PBM.
10/15/2021	No criteria changes with this annual update. Cross references updated to remove an archived policy (dru548).
10/28/2020	Added continuation of therapy (COT) criteria (no change to intent of coverage criteria).
7/24/2019	Added that compounds made for the purpose of convenience is considered not medically necessary.
03/08/2019	Added clarification of compounded implants and pellets, including naltrexone and hormones (such as testosterone, estradiol, etc).
10/04/2018	Added clarification of excluded coverage for compounds containing only excluded products such as bulk chemicals and OTC drugs.
08/17/2018	Added criterion to clarify that if the active ingredient requires pre-authorization, then medical necessity criteria for that medication must also be met.
08/11/2017	No changes to coverage criteria with this annual update.
03/10/2017	No changes to coverage criteria with this annual update.

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Medication Policy Manual | **Policy No:** dru196

Topic: Arzerra, ofatumumab | **Date of Origin:** January 15, 2010

Committee Approval Date: July 16, 2021 | **Next Review Date:** April 2022

Effective Date: October 1, 2021

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Ofatumumab (Arzerra) is a B-cell-directed monoclonal antibody used in the treatment of lymphocytic leukemia (CLL). It is given via intravenous infusion.

Policy/Criteria

Most contracts require pre-authorization approval of ofatumumab (Arzerra) prior to coverage.

I. Continuation of therapy (COT): Ofatumumab (Arzerra) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Ofatumumab (Arzerra) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A and B below are met.

A. Diagnosis of **relapsed or refractory chronic lymphocytic leukemia** (CLL).

AND

B. Clinical documentation (including, but not limited to chart notes) confirming that at least two prior therapies for CLL have been ineffective.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy services does not consider ofatumumab (Arzerra) to be a self-administered medication.

B. When preauthorization is approved, ofatumumab (Arzerra) will be authorized for a single treatment course of up to 12 infusions in a 12-month period. No additional treatment courses will be authorized beyond 12 infusions.

IV. Ofatumumab (Arzerra) is considered not medically necessary for the following conditions:

A. Rheumatoid arthritis (RA).

B. Previously untreated CLL.

V. Use of ofatumumab (Arzerra) beyond a total of 12 infusions is considered investigational. Additionally, ofatumumab (Arzerra) is considered investigational when used for all other conditions, including but not limited to:

A. Non-Hodgkin's follicular lymphoma.

B. Maintenance therapy in CLL.

C. Mucosa-associated lymphoid tissue (MALT) lymphoma.

D. Relapsing-remitting multiple sclerosis (RRMS).

Position Statement

- Ofatumumab (Arzerra) is a monoclonal antibody that is directed against B-lymphocytes. It results in depletion of B-cells by binding to CD20 molecules expressed on the B lymphocytes. Rituximab and obinutuzumab (Gazyva) are also CD20-directed therapies.
- Ofatumumab (Arzerra) is approved for the treatment of chronic lymphocytic leukemia (CLL) when first-line therapies, specifically fludarabine and alemtuzumab, were not effective; as a first-line therapy when given with chlorambucil for patients who are not candidates for fludarabine-based chemotherapy; for relapsed CLL when given with fludarabine and cyclophosphamide; or for maintenance therapy in patients who are in complete or partial response after at least two lines of therapy for recurrent or progressive CLL. (Note: Alemtuzumab is no longer commercially available; however, it is available through the manufacturer at no cost when used for cancer treatment).
- The intent of this policy is to cover ofatumumab (Arzerra) for relapsed or refractory CLL after at least two prior CLL therapies have been ineffective.
- The efficacy of ofatumumab (Arzerra) is based on surrogate endpoints such as tumor response and progression-free survival (PFS). To date, there is no evidence of improved clinical outcomes such as improved survival, quality of life, or symptom control.

- Ofatumumab (Arzerra) has not been directly compared with rituximab or obinutuzumab (Gazyva), two other CD20-directed therapies used in the treatment of CLL. Ofatumumab (Arzerra) has the potential to be the most costly option among these similar treatment options.
- A recent study reported improved PFS with ibrutinib (Imbruvica) relative to ofatumumab (Arzerra) when administered to patients with CLL who had received prior therapy for their disease. The trial was stopped early due to these positive findings for ibrutinib (Imbruvica). Overall survival data from the trial is not mature.
- Although the National Comprehensive Cancer Network (NCCN) Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma guideline lists ofatumumab (Arzerra) as one of many category 2A options in the relapsed or refractory CLL setting, there are several preferred therapies in each of these settings with higher level recommendations (category 1).
- A recent study evaluated ofatumumab (Arzerra) in patients with rheumatoid arthritis who had an inadequate response to methotrexate. There are many other medications with longer track records of safety and effectiveness that provide a better value in this population.
- Ofatumumab (Arzerra) is being studied in other conditions were B-cells may play a role in the disease process. Studies evaluating the possible benefit in these other conditions, which includes follicular lymphoma and multiple sclerosis, are currently ongoing.
- Ofatumumab (Arzerra) is administered via intravenous infusion for a total of 12 infusions. There is not sufficient evidence to support use of ofatumumab (Arzerra) beyond a single course of up to 12 infusions.

Regence Pharmacy Services performs independent analyses of oncology medication evidence. NCCN clinical practice guidelines assignment of a category 2a/b recommendation does not necessarily establish medically necessity. The Regence Pharmacy Services analysis and coverage policy may differ from NCCN clinical practice guidelines.

Clinical Efficacy

OFATUMUMAB (ARZERRA) IN CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

Ofatumumab (Arzerra) has been studied in chronic lymphocytic leukemia (CLL) in the relapsed setting as a single agent, and in the first-line setting in combination with chlorambucil in patients who are not candidates for cytotoxic chemotherapy. To date, there is no evidence that it improves disease-related symptoms or overall survival. Additionally, there is no evidence that it is superior to any other therapy for CLL in any setting.

<u>Relapsed/refractory CLL</u>

- A small, low-quality, single-arm study evaluated tumor response rate as the primary endpoint in 59 patients with relapsed/refractory CLL. [1 2]

    * All patients included in the trial had CLL that was refractory to both fludarabine and alemtuzumab (Campath). The median number of prior therapies was five.
    * The investigator-determined overall response rate (combination of partial and complete responders) was 42%. There were no complete responses.
    * Eighty-eight percent of patients in the clinical trial received at least 8 of the 12 scheduled doses of ofatumumab (Arzerra), while 54% of subjects received all 12 infusions.
    * The evidence from this trial is of low-quality because there was no comparator, the subjects were not blinded or randomized, and the endpoint (tumor response) has not been validated to correlate with clinically relevant outcomes (e.g., overall survival, symptom control, or quality of life).
    * Note: Alemtuzumab (Campath) is no longer commercially available because the manufacturer is now marketing it as a new therapy for multiple sclerosis. However, it is available at no charge through the manufacturer when used for the treatment of cancer. Visit http://www.campath.com/ for details on the Campath Distribution Program.
- A large, randomized, open-label trial compared ibrutinib (Imbruvica) with ofatumumab (Arzerra) in previously treated patients with CLL or small lymphocytic lymphoma (SLL), a related condition. [3]
    * The trial evaluated patients who had received at least one prior therapy (median of 2 to 3) and were not candidates for treatment with a purine analog (e.g., fludarabine) because they had a short progression-free interval after prior chemotherapy, they were of advanced age (≥ 70 years), had a coexisting illness, or had a chromosome 17p13.1 deletion.
    * Patients (N = 391) were randomized in a 1:1 fashion to receive either ibrutinib (Imbruvica) 420 mg orally daily, or a standard course (12 infusions) of ofatumumab (Arzerra). A majority of patients had high-risk features, including del(17p) or del(11p).
    * The median duration of progression-free survival was 8.1 months with ofatumumab (Arzerra) and had not yet been reached in the ibrutinib (Imbruvica) arm (median follow up of 9.4 months). This difference was statistically significant.
    * Survival at 12 months was 90% and 81% in the ibrutinib (Imbruvica) and ofatumumab (Arzerra) treatment arms, respectively. Median overall survival has not been reached in either group.
    * There is low confidence in the comparative evidence from this trial because it was an open-label design and there were differences in baseline characteristics between the two populations [patients in the ibrutinib (Imbruvica) treatment arm were more heavily pretreated and there was a greater proportion of patients with bulky disease in this arm]. Bias due to lack of blinding and poor randomization cannot be ruled out. Additionally, future reports of overall survival will be confounded by crossover from ofatumumab (Arzerra) to ibrutinib (Imbruvica).

- The NCCN CLL/SLL guideline lists ofatumumab (Arzerra) as a category 2A recommendation among 'Other recommended regimens' when used in the relapsed and refractory CLL/SLL setting. There are several alternative regimens (both category 1 and category 2A recommendations) which are listed as preferred regimens. [4]

Not Medically Necessary and Investigational Uses

Previously untreated CLL

- A large, randomized, open-label trial evaluated ofatumumab (Arzerra) plus chlorambucil in patients with CLL who had no previous treatment for their disease. [1 5]
  - The trial evaluated patients who were not candidates for fludarabine-based chemotherapy due to advanced age (≥ 70 years) or presence of comorbidities (e.g., coexisting illness, poor renal function).
  - Patients (N=447) were randomized to ofatumumab (Arzerra) plus chlorambucil or chlorambucil alone. Treatment was given in 28-day cycles for up to 12 cycles.
  - Progression-free survival (PFS), the primary endpoint, was 22.4 months and 13.1 months in the ofatumumab (Arzerra) plus chlorambucil and chlorambucil alone arm, respectively.
  - There were inadequate details available to assess the quality of evidence in this trial; however, the lack of blinding is considered a major flaw.
- The efficacy of ofatumumab (Arzerra) has not been studied beyond a single treatment course which consists of 12 infusions. [1-3]
- Ofatumumab (Arzerra) has not been directly compared with rituximab or obinutuzumab (Gazyva), two additional CD20-directed therapies used in the treatment of CLL.
- The National Comprehensive Cancer Network (NCCN) Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma guideline does not recommend ofatumumab (Arzerra) as first-line therapy for CLL in patients with or without a del(17p)/TP53 mutation. [4]

Maintenance therapy for CLL

- A low-quality, open-label, multicenter, Phase III trial compared ofatumumab (Arzerra) maintenance therapy (1000 mg every 8 weeks for up to 2 years) with observation for patients in remission after reinduction for relapsed CLL. Treatment continued until disease progression or the patient withdrew from the study. [6]
  - At the planned interim analysis, PFS was significantly improved in the ofatumumab (Arzerra) arm (29.4 months) compared to the observation arm (15.2 months).
  - However, there was no significant difference between the treatment arms in OS (HR=0.85; 95% CI, 0.52 to 1.37; p=0.49).
  - No clinically relevant differences in HRQOL were observed.
- The NCCN CLL/SLL guidelines gives ofatumumab (Arzerra) a lower than standard recommendation (category 2B) for CLL maintenance therapy. [4]

Other conditions

- Ofatumumab (Arzerra), an anti-CD20 antibody, has been studied in several other B-cell-mediated conditions.
    * *Follicular lymphoma*: Several trials have evaluated ofatumumab (Arzerra) in follicular lymphoma. [7-9] To date, none of the trials have evaluated a clinical endpoint or compared ofatumumab (Arzerra) to either placebo or any established therapy. Additional studies are needed to establish the safety and effectiveness of ofatumumab (Arzerra) in this condition.
    * *Mucosa-associated lymphoid tissue (MALT) lymphoma:* A preliminary trial in 16 patients suggests that ofatumumab (Arzerra) may have activity in this disease based on objective tumor response rates. A larger, well-designed study is needed to establish safety and effectiveness in this condition. [10]
    * *Rheumatoid arthritis*: One small phase I/II trial and a larger phase III trial evaluated ofatumumab (Arzerra) in patients with rheumatoid arthritis. [11 12] The larger of the two trials compared ofatumumab (Arzerra) with placebo in patients who had an inadequate response to methotrexate. [12] There are many established treatment options with long track records of safety and effectiveness that provide a better value in this population.
    * *Relapsing-remitting multiple sclerosis (RRMS)*: A small, published, phase II, dose-finding, cross-over trial evaluated MRI lesions and B-cell counts in patients receiving ofatumumab (Arzerra) for RRMS for 24 weeks. Standard trial design to establish safety and efficacy of medications in RRMS includes evaluation of MS attack rate in hundreds of patients over a minimum of 2 years. Larger, well-controlled trials evaluating a clinical endpoint are needed to establish ofatumumab (Arzerra) as a safe and effective therapy for RRMS. [13]
    * *Waldenström's macroglobulinemia (WM)*: There is interest in using ofatumumab (Arzerra) in WM by virtue of its mechanism of action which is similar to other therapies used in the treatment of this condition; however, to date, no clinical trials have been published to support this use.
- The NCCN compendium lists ofatumumab (Arzerra) among many category 2A recommendations for Waldenström's macroglobulinemia. Its use is recommended only in rituximab -intolerant individuals. [14] No clinical trials were identified that evaluated ofatumumab (Arzerra) in this condition.

Safety [1]

- Infections, neutropenia, and fever are the most common serious adverse reactions observed with ofatumumab (Arzerra).
- Ofatumumab (Arzerra) may cause serious infusion reactions leading to symptoms that include bronchospasm, dyspnea, laryngeal edema, cardiac infarction, and angioedema. Premedication with intravenous corticosteroids, an oral analgesic, and on oral or intravenous antihistamine are recommended before infusing.
- Ofatumumab (Arzerra) has a boxed warning to highlight the potential risk of progressive multifocal leukoencephalopathy (PML) and reactivation of hepatitis B.

Dosing [1]

- Relapsed CLL: Ofatumumab (Arzerra) is administered for up to 6 cycles as follows:
  - 300 mg on Day 1, followed by 1,000 mg on Day 8 (Cycle 1)
  - 1,000 mg on Day 1 of subsequent 28-day cycles for a maximum of 6 cycles.
- Refractory CLL: Ofatumumab (Arzerra) is administered in 12 doses as follows:
  - An initial dose of 300 mg (Dose 1), followed one week later by
  - 2,000 mg weekly for 7 doses (Doses 2 through 8), followed 4 weeks later by
  - 2,000 mg every four weeks for 4 doses (Doses 9 through 12).
- Premedicate before each dose with acetaminophen, an oral or intravenous antihistamine, and an intravenous corticosteroid (prednisolone 100 mg or equivalent).
- The safety and effectiveness of ofatumumab (Arzerra) have only been formally evaluated based on the administration of a single, 12-dose course of therapy. Although there is a published case series of a small subset of subjects from the pivotal trial who went on to receive a second course of ofatumumab (Arzerra) when their CLL progressed after an initial 12-dose course, this low-level evidence is not sufficient to support the benefit of this practice versus changing to an alternative therapy. [15]

Appendix 1: CD20-Directed Therapies for Chronic Lymphocytic Leukemia (CLL)
Obinutuzumab (Gazyva)
Ofatumumab (Arzerra)
Rituximab

Cross References
Copiktra, duvelisib, Medication Policy Manual, Policy No. dru573
Gazyva, obinutuzumab, Medication Policy Manual, Policy No. dru327
Imbruvica, ibrutinib, Medication Policy Manual, Policy No. dru326
Non-Preferred Products with Therapeutically Interchangeable Biosimilars/Reference Products, Medication Policy Manual, Policy No. dru620
Venclexta, venetoclax, Medication Policy Manual, Policy No. dru462
Zydelig, idelalisib, Medication Policy Manual, Policy No. dru363

Codes	Number	Description
HCPCS	J9302	Injection, ofatumumab (Arzerra), 10 mg

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Revision History

Revision Date	Revision Summary
7/16/2021	No criteria changes with this annual update.
06/15/2020	Removed references to brand Rituxan from policy, to account for upcoming changes in biosimilars policy (dru620).
4/22/2020	Added continuation of therapy (COT) criteria (no change to intent of coverage criteria).
4/25/2019	Mucosa-associated lymphoid tissue (MALT) lymphoma was added to the list of investigational conditions.
3/19/2018	No changes to coverage criteria with this annual update.
1/13/2017	Revised coverage criteria to specify relapsed or refractory CLL. Added maintenance therapy as an investigational use.
1/8/2016	No changes with this annual update.
1/15/2010	New policy

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Medication Policy Manual

Policy No: dru198

Topic: Istodax, romidepsin

Date of Origin: January 15, 2010

Committee Approval Date: July 16, 2021

Next Review Date: April 2022

Effective Date: October 1, 2021

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Romidepsin (Istodax), a histone deacetylase (HDAC) inhibitor, is a cancer medication used in the treatment of certain T-cell lymphomas. It is given via intravenous infusion.

Policy/Criteria

Most contracts require pre-authorization approval of romidepsin (Istodax) prior to coverage.

I. Continuation of therapy (COT): Romidepsin (Istodax) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Romidepsin (Istodax) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) confirming that criterion A or B below is met.

A. A diagnosis of **peripheral T-cell lymphoma** (PTCL) when at least two prior systemic therapies have been ineffective or not tolerated (see *Appendix 1* for therapy options).

OR

B. A diagnosis of **cutaneous T-cell lymphoma** (CTCL) [e.g. Mycosis Fungoides and Sézary Syndrome] when at least two prior systemic therapies have been ineffective or not tolerated (see *Appendix 2* for therapy options).

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services does not consider romidepsin (Istodax) to be a self-administered medication.

B. When pre-authorization is approved, romidepsin (Istodax) will be authorized for up to three infusions every four weeks until disease progression.

C. Authorization may be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

IV. Romidepsin (Istodax) is considered investigational when used in patients who have had prior treatment with belinostat (Beleodaq) and when used in combination with other chemotherapy medications.

V. Romidepsin (Istodax) is considered investigational when used for all other conditions, including but not limited to:

A. Prostate cancer.

B. Squamous cell cancer of the head and neck (SCCHN).

C. Solid tumors.

Position Statement

- Romidepsin (Istodax), a histone deacetylase (HDAC) inhibitor, is among several systemic medications (see *Appendices 1 and 2*) that may be used to treat cutaneous T-cell lymphoma (CTCL) [e.g. Mycosis Fungoides (MF), Sézary Syndrome (SS)] and peripheral T-cell lymphoma (PTCL).
  - The intent of this policy is to cover romidepsin (Istodax) for the indications and dose for which it has been shown to be safe and effective, as detailed in the coverage criteria.
- The effectiveness of romidepsin (Istodax) is based on low-quality, single-arm studies that evaluated tumor response rates, a surrogate marker, as the primary endpoint.
- The effect of these therapies on overall survival has not been evaluated.
- Romidepsin (Istodax) has not been studied in the first-line setting nor has it been compared to any other therapy options.
- Romidepsin (Istodax) is administered via intravenous infusion over 4 hours and is given until disease progression or unacceptable toxicity.

Regence Pharmacy Services performs independent analyses of oncology medication evidence. NCCN clinical practice guidelines assignment of a category 2a/b recommendation does not necessarily establish medically necessity. The Regence Pharmacy Services analysis and coverage policy may differ from NCCN clinical practice guidelines.

Clinical Efficacy

Cutaneous T-cell Lymphoma (CTCL)

- The effectiveness of romidepsin (Istodax) has been evaluated in 167 subjects with cutaneous T-cell lymphoma (CTCL) in two, uncontrolled clinical trials with poor quality evidence. [1-3]
  - There was no comparator in either of the studies.
  - The studies evaluated a subgroup of subjects with CTCL for overall response (partial response plus complete response) to therapy.
  - Approximately 34% of subjects had either a partial response (28%) or a complete response (6%).
- All subjects evaluated in the studies had been on one or more prior systemic therapies.
- There is currently no evidence that romidepsin (Istodax) improves clinical outcomes (e.g. overall survival, quality of life) in patients with CTCL.

Peripheral T-cell Lymphoma (PTCL)

- Romidepsin (Istodax) was evaluated in 130 patients with PTCL who had failed at least one prior therapy. The evidence is of poor quality as the trial was not controlled. [4] A second trial in a mixed group of patients with PTCL or CTCL was used as supportive information. [5]
  - Romidepsin (Istodax) was not compared with placebo or an active comparator in either study.
  - The primary endpoint evaluated was disease response rate which is based on disease markers. Clinical outcomes, such as survival, have not been evaluated.
  - The overall response rate (complete response rate plus partial response rate) was 25% with 15% of patients achieving a complete response. [4]
- All subjects evaluated in the studies had been on one or more prior systemic therapies. [4,5]
- There is currently no evidence that romidepsin (Istodax) improves clinical outcomes (e.g. overall survival, quality of life) in patients with PTCL.

National Guidelines

- The National Comprehensive Cancer Network (NCCN) T-cell lymphomas and Primary Cutaneous Lymphomas guidelines lists romidepsin (Istodax) among several recommended systemic treatment options for the treatment of both CTCL and PTCL. [6,7] [refer to *Appendix 1* and *Appendix 2*].

Use in Other Conditions

- Romidepsin (Istodax) is being evaluated for use in several other conditions:
  - Preliminary studies failed to demonstrate a benefit in advanced colorectal cancer, metastatic renal cell carcinoma, prostate cancer, and lung cancer. [8-12]
  - A phase 2 study evaluated the combination of romidepsin (Istodax) and gemcitabine in patients with relapsed or refractory PTCL. There was no additional benefit shown over the use of romidepsin (Istodax) alone. [13]
  - In small number of patients with relapsed multiple myeloma, poor response rates were achieved. [14]

* No results are available for studies in several other conditions including squamous cell cancer of the head and neck (SCCHN), breast cancer, solid tumors, and acute myelogenous leukemia. [15]

Safety [1]

- The most common adverse experiences reported with romidepsin (Istodax) include: nausea, fatigue, infections, vomiting, anorexia, bone marrow depression, low serum magnesium, diarrhea, fever, and hypotension.
- Prolongation of the QT interval and increased risk of serious infections have been reported with romidepsin.
- There is the potential for clinically significant drug-drug interactions when romidepsin (Istodax) is co-administered with strong CYP 3A4 inhibitors (e.g. ketoconazole, clarithromycin) and inducers (e.g. rifampin), as well as with drugs that inhibit the P-glycoprotein pathway (e.g. cyclosporine).
- Caution is urged when co-administering romidepsin (Istodax) with warfarin, as elevations in INR may occur.

Dosing considerations [1]

- Romidepsin (Istodax) is administered intravenously on days 1, 8, and 15 of every 28-day cycle until disease progression or unacceptable toxicity. [1]
- Dose adjustment may be necessary for hematologic as well as nonhematologic toxicities. [1]

Appendix 1: Systemic Treatment Options for PTCL [6] a,b,c

First-line Therapy

- Brentuximab vedotin + CHP (cyclophosphamide, doxorubicin, prednisone) for CD30+ histologies
- CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone)
- CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)
- CHOP followed by IVE (ifosfamide, etoposide, epirubicin) alternating with methotrexate
- EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)
-

Second-line Therapy

Transplant candidates	*Non-transplant candidates*
• *Preferred single agents:* o Belinostat (Beleodaq) o Brentuximab vedotin (Adcetris) for CD30+ PTCL o Pralatrexate (Folotyn) o Romidepsin (Istodax) • *Preferred combination regimens:* o DHAP (dexamethasone, cisplatin, cytarabine) o DHAX (dexamethasone, oxaliplatin, cytarabine) o ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) o GDP (gemcitabine, dexamethasone, cisplatin) o GemOx (gemcitabine, oxaliplatin) o ICE (ifosfamide, carboplatin, etoposide) • *Other recommended therapies:* o Bendamustine o Gemcitabine o Lenalidomide o GVD (gemcitabine, vinorelbine, liposomal doxorubicin)	• *Preferred Single agents:* o Belinostat (Beleodaq) o Brentuximab vedotin (Adcetris) for CD30+ PTCL o Pralatrexate (Folotyn) o Romidepsin (Istodax) • *Other single agents:* o Alemtuzumab (Campath) o Bendamustine o Cyclophosphamide and or etoposide (IV or PO) o Gemcitabine o Lenalidomide (Revlimid) o Radiation therapy

[a] PTCL subtypes included: PTCL not otherwise specified (NOS), angioimmunoblastic T-cell lymphoma (AITL), anaplastic large cell lymphoma (ALCL), and enteropathy-associated T-cell lymphoma (EATL)

[b] All therapies listed above are NCCN category 2A recommendations (lower quality evidence but uniform consensus among panel) unless otherwise indicated.

[c] AITL and ALCL have slight variations in the regimens used in the second line and subsequent therapy setting

Appendix 2: Systemic Treatment Options* for CTCL (i.e. Mycosis Fungoides/Sezary syndrome) [7]	
acitretin (Soriatane)	interferon gamma (Actimmune)
alemtuzumab (Campath)	isotretinoin
all-trans retinoic acid (Vesanoid)	methotrexate
bexarotene (Targretin)	mogamulizumab (Poteligeo)
brentuximab vedotin (Adcetris)	pembrolizumab (Keytruda) [category 2B]
chlorambucil (Leukeran)	pentostatin
cyclophosphamide	pralatrexate (Folotyn)
doxorubicin, liposomal (Doxil)	romidepsin (Istodax)
etoposide	temozolomide (CNS involvement)
gemcitabine	vorinostat (Zolinza)
interferon alfa (Intron A)	

* All therapies listed above are NCCN category 2A recommendations (lower quality evidence but uniform consensus among panel), unless otherwise noted.

Cross References
Adcetris, brentuximab, Medication Policy Manual, Policy No. dru264
Beleodaq, belinostat, Medication Policy Manual, Policy No. dru362
Folotyn, pralatrexate, Medication Policy Manual, Policy No. dru197

Codes	Number	Description
HCPCS	J9315	Injection, romidepsin (Istodax), 1 mg

References

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Revision History

Revision Date	Revision Summary
7/16/2021	No criteria changes with this annual update.
4/22/2020	Added continuation of therapy (COT) criteria (no change to intent of coverage criteria).
4/25/2019	No criteria changes with this annual update.
7/20/2018	• Clarify quantity limit (up to three infusions every four weeks until disease progression). • Updated criteria with standard policy language (no changes to intent).
7/14/2017	No criteria changes with this annual update.
9/9/2016	No criteria changes with this annual update.
1/15/2010	New policy

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Medication Policy Manual

Policy No: dru216

Topic: Provenge, sipuleucel-T

Date of Origin: August 11, 2010

Committee Approval: June 20, 2024

Next Review Date: 2025

Effective Date: September 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Provenge (sipuleucel-T) is indicated for the treatment of asymptomatic or minimally symptomatic metastatic, castration-resistant prostate cancer. It is an immunotherapy derived from a patient's own immune cells and is designed to stimulate an immune response against the prostate cancer.

Policy/Criteria

Most contracts require pre-authorization approval of Provenge (sipuleucel-T) prior to coverage.

I. Continuation of therapy (COT): Provenge (sipuleucel-T) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Provenge (sipuleucel-T) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A through F below are met.

A. Diagnosis of **metastatic adenocarcinoma of the prostate**.

AND

B. Radiographic evidence of metastases beyond the primary tumor, (such as bone and soft tissue) except visceral metastases; specifically, liver, lung, or brain metastases. [1]

AND

C. Hormone refractory (also known as castration-resistant, castration-recurrent, or androgen-independent) disease when both criteria 1 and 2 below are met:

1. Disease progression or metastasis despite removal of testes OR despite treatment with anti-androgen medications such as Lupron (leuprolide).

AND

2. Current testosterone level is < 50 ng/dL.

AND

D. Asymptomatic or minimally symptomatic disease [e.g., no narcotic (opioid) use for prostate cancer-related pain].

AND

E. If cytotoxic chemotherapy [e.g., docetaxel, cabazitaxel] has been previously administered, it must have been stopped for at least 3 months prior to initiation of leukapheresis for Provenge (sipuleucel-T) therapy.

AND

F. If immunosuppressants such as systemic corticosteroids at doses > 5 mg prednisone or equivalent) and/or radiation have been administered, it must have been stopped for at least 28 days prior to initiation of leukapheresis for Provenge (sipuleucel-T) therapy.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Provenge (sipuleucel-T) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Provenge (sipuleucel-T) may be authorized one-time for a maximum of three infusions, each of which includes harvest and re-infusion of activated leucocytes. When criteria for coverage are met, up to 3 completed infusions (one course of therapy) may be authorized per lifetime.

C. Additional courses of therapy are considered investigational.

IV. Provenge (sipuleucel-T) is considered investigational when used for all other conditions, including but not limited to:

A. Localized (non-metastatic) prostate cancer.

B. Treatment of patients with moderate to severe prostate cancer-related pain that requires treatment with opioid analgesics.

C. Treatment of metastatic prostate cancer when there is metastasis to the liver, lung, or brain with or without additional metastases.

D. Concomitant use with of either chemotherapy or immunosuppressive agents (such as systemic corticosteroids) with the leukapheresis procedure or Provenge (sipuleucel-T).

Position Statement

- Provenge (sipuleucel-T) may improve overall survival as a first-line therapy in men with metastatic castration-resistant (mCRPC). However, there is uncertainty as to the magnitude of its benefit and its effectiveness relative to docetaxel. [1,2]
- Medical or surgical castration (hormonal intervention) is considered first-line therapy for patients with metastatic prostate cancer. Approximately 15% of patients do not respond to or eventually become refractory to hormonal intervention. [3]
- Docetaxel plus prednisone is considered first-line salvage therapy in patients with mCRPC based on its overall survival advantage over mitoxantrone plus prednisone, a chemotherapy regimen used for palliative treatment. [3]
- In the Provenge (sipuleucel-T) clinical trials, the population studied had radiologically confirmed mCRPC which was asymptomatic or minimally symptomatic. No data exists for its use in moderately or severely symptomatic patients, and it has not been studied in patients with visceral metastases. [1]
- Patients in the clinical trials had castration levels of serum testosterone below 50 ng/dL and a serum PSA of at least 5.0 ng/mL. Disease progression was based on imaging studies or PSA measurements, despite surgical or medical castration. [1,2]
- Pain related to prostate cancer is considered a prognostic factor in metastatic prostate cancer and people with pain tend to have higher tumor burden. [4]
- The use of either chemotherapy or immunosuppressive agents (such as systemic corticosteroids) given at the same time with the leukapheresis procedure for Provenge (sipuleucel-T) has not been studied. Provenge (sipuleucel-T) is designed to stimulate the immune system so simultaneous use of immunosuppressive agents may alter the effectiveness and/or safety of Provenge (sipuleucel-T). [2,5]

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy

- The evidence for Provenge (sipuleucel-T) in the first-line salvage treatment of mCRPC is unreliable. The magnitude of survival benefit relative to placebo is uncertain. [1,2]
- The efficacy of Provenge (sipuleucel-T) relative to docetaxel, another potential first-line therapy in this setting, has not been studied. [2] There are three studies that compared Provenge (sipuleucel-T) with "placebo" (Note: a large proportion of subjects initially randomized to placebo crossed over to a product similar to Provenge (sipuleucel-T) after progression of disease). [1,6,7]
- The evidence from one pivotal published randomized controlled published trial comparing Provenge (sipuleucel-T) with placebo in men with mCRPC disease. At a median follow-up of 34 months, patients who received Provenge (sipuleucel-T) had a statistically significant improvement in overall survival. This trial was appraised as unreliable for reasons that included: [1]
    * Unblinding, which was allowed after disease progression was confirmed.
    * Crossover to alternative therapies after disease progression was allowed at the discretion of the investigator. (This occurred in a large proportion of subjects).
- Both of these flaws may impact the overall survival endpoint. The follow up use of a product similar to Provenge (sipuleucel-T) in the placebo treatment arm has the potential to improve survival in these patients, while follow up use of docetaxel in the Provenge (sipuleucel-T) treatment arm has the potential to improve survival in these patients. This crossover allows for confounding variables and makes it difficult to assess whether the reported overall survival benefit is valid and, if the benefit is real, to quantify the benefit.
- The evidence from two smaller published trials comparing Provenge (sipuleucel-T) with placebo in men with mCRPC disease were appraised as not reliable for reasons that included: [6,7]
    * Use of time to progression (TTP) of disease as a primary endpoint. TTP does not predict overall survival, a clinically relevant endpoint, in men with mCRPC.
    * Crossover to other therapies was allowed after progression of disease.
    * Post hoc analysis of overall survival (did not define statistical methods in advance).
    * One study was stopped before it met its enrollment goal.
- Provenge (sipuleucel-T) is recognized in the National Comprehensive Cancer Network (NCCN) prostate cancer guidelines as a category 1 recommendation ("Useful in certain circumstances") for men with mCRPC with asymptomatic or minimally symptomatic disease with ECOG scores of 0 to 1, and is not recommended for patients with visceral metastases and a life expectancy of less than 6 months. It is also recommended as category 2A in patients who have failed first-line therapy for metastatic disease. [3]

Safety [4]

- The most common adverse reactions include: chills, fatigue, fever, back pain, nausea, joint ache, and headache. There are no published head-to-head clinical trials to support the claim that Provenge (sipuleucel-T) has less toxicity than docetaxel.
- There were more cerebrovascular events (CVEs), including hemorrhagic and ischemic strokes, reported in patients receiving Provenge (sipuleucel-T) than placebo (3.5% vs. 2.6%). The difference was not statistically significant. Nevertheless, the Food and Drug Administration listed it as a safety concern in their review of the safety of this medication.

Cross References
BlueCross BlueShield Association Medical Policy, 8.01.53 - Cellular Immunotherapy for Prostate Cancer. [August 2022]

Codes	**Number**	**Description**
HCPCS	Q2043	Sipuleucel-T (Provenge), minimum of 50 million autologous CD54+ cells activated with PAP-GM-CSF, including leukapheresis and all other preparatory procedures, per infusion

References

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Revision History

Revision Date	Revision Summary
6/20/2024	No criteria changes with this annual review.
12/7/2023	No criteria changes with this annual review.
12/9/2022	• Updated standard language in policy. • No changes to coverage criteria with this annual update.
1/20/2021	Updated continuation of therapy (COT) language. No changes to coverage criteria.
1/22/2020	Added continuation of therapy (COT) criteria (no change to intent of coverage criteria).
1/31/2018	No changes to coverage criteria with this annual update (criteria wording modifications for clarity. No change to intent).
3/19/2018	No criteria changes with this annual update
1/13/2017	No criteria changes with this annual update
1/8/2016	Reorganization of criteria, including splitting some individual criteria into two criteria, for clarity and ease of use. The intent of the policy has not changed.
8/11/2010	New policy.

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Medication Policy Manual | **Policy No:** dru223

Topic: Prolia, denosumab | **Date of Origin:** August 11, 2010

Committee Approval Date: September 19, 2024 | **Next Review Date:** 2025

Effective Date: December 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Prolia (denosumab) is a medication used to treat osteoporosis (bone loss). It works by preventing bone resorption (breakdown). Reducing bone resorption leads to a favorable increase in bone mass and reduction in fracture risk.

PLEASE NOTE: Denosumab is also marketed as Xgeva and is used to prevent skeletal complications of bone metastases from solid tumor cancers. In addition, Xgeva (denosumab) is used for the treatment of giant cell tumor of the bone and hypercalcemia of malignancy. There is a separate medication policy for Xgeva (denosumab) for these indications, specifically.

Policy/Criteria

Most contracts require pre-authorization approval of Prolia (denosumab) prior to coverage.

I. Continuation of therapy (COT): Prolia (denosumab) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, full policy criteria must be met for coverage.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New Starts (Treatment-naïve patients): Prolia (denosumab) may be considered medically necessary when there is clinical documentation (including, but not limited to, chart notes) that criteria A and B below are met.

A. Patients at high risk for fracture defined by meeting any one of criterion 1 through 6:

1. Have a bone mineral density that is 2.5 or more standard deviations below that of a "young normal" adult (T-score at or below –2.5).

OR

2. Have osteopenia (T-score between -1 and -2.5) and glucocorticoid use for at least 3 months at a dose of 5 mg per day or greater, of prednisone (or equivalent).

OR

3. History of osteoporotic (fragility) fracture.

OR

4. Men receiving androgen deprivation therapy (ADT) for nonmetastatic prostate cancer.

OR

5. Women receiving adjuvant aromatase inhibitor therapy for breast cancer.

OR

6. The probability is ≥ 20% for an occurrence of a major osteoporotic fracture or ≥ 3% for hip fracture, based on the US-adapted WHO algorithm Fracture Risk Assessment Tool (FRAX tool).

AND

B. One of the following criterion (1 or 2) below is met:

1. The patient is at very high risk of fracture, defined as meeting one of the following criterion (a through d) below:

a. A history of multiple fragility fractures.

OR

b. A bone mineral density that is 3 or more standard deviations below that of a "young normal" adult (T score at or below - 3.0) with or without fracture history.

OR

c. A bone mineral density that is 2.5 or more standard deviations below that of a "young normal" adult (T score at or below -2.5) **and** a history of at least one fragility fracture.

OR

d. A bone mineral density that is 2.5 or more standard deviations below that of a "young normal" adult (T score at or below -2.5) after completion of a full course of an anabolic bone medication (as listed in *Appendix 1*).

OR

2. Step therapy with lower-cost alternatives has been ineffective, not tolerated or contraindicated as defined by at least one of the following (a through e):

a. The patient has received at least three years of bisphosphonate therapy and remains at high risk for fracture (e.g., T-score at or below –2.5).

OR

b. A bisphosphonate has been ineffective (e.g., a loss of BMD after at least 12 months of treatment or fracture while on treatment).

OR

c. Raloxifene has not been effective after at least a 24-month treatment period based on objective documentation.

OR

d. Bisphosphonates (both oral and IV) are not tolerated due to documented clinical side effects.

OR

e. Bisphosphonates (both oral and IV) are contraindicated based on current medical literature and objective documentation describing the contraindication is provided (including, but not limited to, creatinine clearance of less than 35 ml/min).

PLEASE NOTE: In patients with underlying GI issues, use of oral bisphosphonates may be contraindicated or not tolerated. However, use of an IV bisphosphonate must be trialed for above criterion to be met.

IV bisphosphonates, such as zoledronic acid (generic Reclast), are available for coverage without pre-authorization.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Prolia (denosumab) coverable under the pharmacy benefit (as a self-administered medication) OR coverable under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved Prolia (denosumab) will be authorized in quantities of two 60 mg injections per year.

C. Authorization **may** be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

IV. Prolia (denosumab) is considered not medically necessary for the prevention of skeletal complications of bone metastases from solid tumor cancers, treatment of giant cell tumor of the bone, and hypercalcemia of malignancy.

V. Prolia (denosumab) is considered investigational when used for all other conditions, including but not limited to:

A. Prevention of postmenopausal osteoporosis

B. Use in combination with anabolic bone medications, including but not limited to, Tymlos (abaloparatide), teriparatide (Forteo), or Evenity (romosozumab).

Position Statement

Summary

- Prolia (denosumab) is a monoclonal antibody used for the treatment of osteoporosis in men and postmenopausal women at high risk for fracture (e.g., T-score at or below -2.5, osteopenia and glucocorticoid use for > 3 months, probability ≥ 20% for an occurrence of a major osteoporotic fracture or ≥ 3% for hip fracture based on FRAX tool). In addition, it is used to increase bone mass in patients at high risk for fracture as a result of receiving androgen deprivation therapy for prostate cancer or aromatase inhibitor therapy for breast cancer.

- Bisphosphonate treatment for prevention of bone loss, regardless of cause, is the standard of care due to the body of evidence supporting efficacy and track record of safety. There are both oral and injectable bisphosphonates available as low-cost generics.
- Osteoporosis guidelines consider either oral or injectable bisphosphonates (including alendronate, risedronate, and zoledronic acid), along with Prolia (denosumab), as first-line therapy options for most patients who are candidates for treatment. All of these options have "broad spectrum" anti-fracture activity, with proven efficacy to reduce hip, non-vertebral, and spine fractures. Because raloxifene, a selective estrogen receptor modifier (SERM), has not been shown to reduce hip or non-vertebral fracture, it is considered an alternate to the bisphosphonates and Prolia (denosumab). [1]
- American Association of Clinical Endocrinologists (AACE) guidelines recommend that Tymlos (abaloparatide), Prolia (denosumab), Evenity (romosozumab), teriparatide (Forteo), and zoledronate as initial therapy for patients at very high fracture risk. The definition for very high risk differs in in Endocrine Society and AACE guidelines but both include patients with a T-score at or below -2.5 and a history of fracture, or a history of multiple fractures. [1 2] An additional definition of very high risk in the AACE guidelines includes patients with a T-score at or below -3.0, regardless of fracture history.
- There is consistent evidence that Prolia (denosumab) is a potent antiresorptive therapy. The effect is consistent across the placebo-controlled trials and comparative, non-inferiority trials. Prolia (denosumab) has demonstrated the potential to decrease the risk of fractures in patients with osteoporosis to a similar degree as other established treatment options (e.g., bisphosphonates); however, it is unknown if Prolia (denosumab) is a superior treatment option.
- Comparative evidence evaluating Prolia (denosumab) and bisphosphonates for osteoporosis assessed bone mineral density (BMD) as the primary endpoint, which is not as clinically relevant as the ability to prevent fracture.
- There is no comparative evidence evaluating Prolia (denosumab) and bisphosphonates for the prevention of osteoporosis associated with hormone suppression treatment in breast or prostate cancer.
- Generic treatments, such as bisphosphonates (oral and injectable), provide the best value for the prevention or treatment of bone loss in high-risk patients. Prolia (denosumab) has not been proven to be safer or more effective than generic bisphosphonates but is more costly. For patients unable to use oral bisphosphonates due to gastrointestinal (GI) issues, IV bisphosphonates are a treatment option as they do not have direct GI irritant effects.
- Denosumab is also marketed as Xgeva and is indicated for the treatment of skeletal complications of bone metastases from solid tumor cancers, treatment of giant cell tumor of the bone, or hypercalcemia of malignancy. Use of Prolia for these indications is considered not medically necessary as dosage and frequency of administration differ between indications and products.
- The use of Prolia (denosumab) for the prevention of postmenopausal osteoporosis is considered investigational as there is no evidence supporting its safety and efficacy in

this population. A number of other therapies (e.g., lifestyle modifications, calcium and vitamin D, bisphosphonates) may be appropriate in select patients.

- In addition, there is insufficient evidence to establish that the use of Prolia (denosumab) in combination with anabolic agents, such as teriparatide (Forteo) or Tymlos (abaloparatide), is more effective than monotherapy with either agent.
- Although the risk for osteonecrosis of the jaw (ONJ) and atypical femoral fracture (AFF) may be increased with long-term bisphosphonate use, the absolute risk reduction of clinical fractures with these medications are far greater than the absolute risk of AFF and ONJ. [3]
- The 2019 Endocrine Society Osteoporosis guideline and American Society for Bone and Mineral Research (ASBMR) recommend post-menopausal women be evaluated for fracture risk after 3-5 years of bisphosphonates. Patients with low-moderate fracture risk may consider a drug holiday, which is defined as a period of time when no osteoporosis medications are given. For patients with high risk (which include multiple spine fractures or hip/spine BMT $\leq$-2.5) osteoporosis treatment should be continued, as the benefits likely outweigh potential harms. [4]
- The 2019 Endocrine Society guidelines also recommend dual-energy X-ray absorptiometry (DEXA) at the spine and hip every 1 to 3 years to assess the response to treatment. While there is uncertainty regarding what is considered an adequate response, guidelines state the stable or increasing BMD may indicate a good response. Switching treatments may also be considered in patients who experience a fracture. [4]
- There have not been adequate studies to evaluate the efficacy of switching to alternative therapies and the optimal duration of bisphosphonate therapy is unclear.

Clinical Efficacy

Osteoporosis

- Prolia (denosumab) has not been proven in reliable clinical studies to be more effective than generic options.
- There are several randomized controlled trials (RCTs) assessing the efficacy of Prolia (denosumab) relative to placebo or alendronate. [5-8] However, only one trial studied the clinically meaningful endpoint of fracture prevention. [7] The other efficacy trials used percent change in bone mineral density (BMD) or geometric parameters as the primary endpoint. [5 6 8 9] BMD is a surrogate marker and change in BMD is poorly correlated to fracture prevention. Furthermore, geometric parameters remain a research method versus a clinical technique.
    - ***** A single trial established the efficacy of Prolia (denosumab) with regard to decreased fracture risk in postmenopausal osteoporosis compared to placebo. [7]
    - ***** Prolia (denosumab) reduces the risk of vertebral, hip and non-vertebral fractures in post-menopausal women with osteoporosis over 36 months when compared to placebo.
    - ***** Data from the long-term extension are available. Reduction in bone turnover and increases in BMD were maintained over time with Prolia (denosumab); however,

due to the cross-over design of the trial, the benefit for reducing fracture risk beyond 36 months of treatment cannot be determined. [10 11]

- There are trials comparing Prolia (denosumab) to weekly alendronate for the treatment of osteoporosis in post-menopausal women; however, there are limitations to these data.
  * The primary endpoint of many of these trials is BMD changes at 12 months, which is not as clinically relevant as fracture data. [5 6]
  * Another study performed a post-hoc analysis of a subset of patients (n = 116) enrolled in a phase 2 dose-ranging study. The primary endpoint of this study was geometric strength parameters. Although the effects of Prolia (denosumab) were greater than alendronate in select bone sites, the results are only suggestive of a correlation to improved fracture data and do not definitively prove that Prolia (denosumab) is superior to alendronate for preventing osteoporosis-related fractures. [9]
- The FRAX tool (www.shef.ac.uk/FRAX) was developed by the World Health Organization (WHO) to evaluate fracture risk of patients. It integrates clinical risk factors with BMD at the femoral neck. The FRAX tool provides the 10-year probability of fracture. The output is a 10-year probability of hip fracture and the 10-year probability of a major osteoporotic fracture (forearm, shoulder, or clinical vertebral fracture).
- Treatment should be considered if the 10-year risk is 3% or more for hip fracture or 20% or more for "major" osteoporosis-related fracture based on the US-adapted WHO algorithm (FRAX tool). [12]
- 2019 Endocrine Society Osteoporosis guideline recommend initial treatment with bisphosphonates (alendronate, risedronate, zoledronic acid, and ibandronate). They are available at low cost and have a long history of use. Prolia (denosumab) is considered an alternative initial treatment for patients who are not candidates for a bisphosphonate or who have not had an adequate response to bisphosphonates[4]
- An injectable option [e.g., zoledronic acid, Prolia (denosumab), Evenity (romosozumab), Tymlos (abaloparatide), or teriparatide (Forteo)] is recommended for those with a prior fragility fracture or indicators of higher fracture risk (e.g., advanced age, frailty, glucocorticoids, very low T-scores, or increased fall risk); however, no one specific injectable option is preferred over another. [12] Of the treatment options, generic zoledronic acid is the lowest cost treatment choice.
- The evidence for combination use of Prolia (denosumab) and teriparatide (Forteo) is limited to one small trial in post-menopausal women (n = 94). Although the combination resulted in a larger increase in BMD than either agent alone, there are no fracture data available. [13] Combination therapy substantially raises the cost and probably increases the potential for side effects. Until the effect of combination therapy on fracture is better understood, the AACE/ACE does not recommend concomitant use of these agents. [1 2]

Prevention of Osteoporosis due to Hormone Suppression

- For prostate cancer and breast cancer patients on hormone suppression therapy, hormone suppression increases bone turnover and decreases bone mineral density.
- There is a limited body of evidence for fracture prevention during hormone suppression therapy for prostate cancer and breast cancer. Trials were designed to demonstrate an

increase in BMD or time to first fracture, rather than a reduction in fracture risk. BMD is a surrogate for fracture risk, a more clinically meaningful measure of efficacy. The effect of Prolia (denosumab) on overall survival remains unknown.

Prostate Cancer

* For the treatment of bone loss in men with prostate cancer receiving androgen deprivation therapy (ADT), the evidence for efficacy for Prolia (denosumab) comes from a randomized, placebo-controlled trial in men with nonmetastatic prostate cancer. [14]
* Following two years of treatment, the lumbar spine BMD was higher in Prolia (denosumab)-treated patients compared to placebo-treated patients. Prolia (denosumab) also significantly reduced the incidence of new vertebral fractures (a secondary endpoint) at three years.
* In addition to Prolia (denosumab), there is evidence that pamidronate, zoledronic acid, and alendronate increase BMD during ADT for prostate cancer.
* There is no comparative evidence between bisphosphonates or Prolia (denosumab) for prevention of osteoporosis due to hormone suppression in patients with prostate cancer.
* The National Comprehensive Cancer Network (NCCN) Prostate Cancer guideline recognizes both Prolia (denosumab) and bisphosphonates (zoledronic acid or alendronate) to increase bone density, a surrogate for fracture risk in men without metastases receiving ADT. Treatment with any of these agents is recommended when the absolute fracture risk warrants drug therapy, with no preference for one agent over another.[15]

Breast Cancer

* For the treatment of bone loss in women with breast cancer receiving adjuvant aromatase inhibitor therapy, the evidence for efficacy for Prolia (denosumab) comes from a randomized, placebo-controlled trial. [16] Following one year of treatment, the lumbar spine BMD was higher in Prolia (denosumab)-treated patients compared to placebo-treated patients.
* Another study (ABCSG-18) evaluated the effects of Prolia (denosumab) relative to placebo on time to first clinical fracture in postmenopausal, aromatase inhibitor-treated patients with early-stage hormone receptor-positive breast cancer. [17] Compared to placebo, patients treated with Prolia (denosumab) had a significantly delayed time to first clinical fracture.
* There is no evidence that that Prolia (denosumab) is superior to intravenous bisphosphonates in the early breast cancer setting.
    - Prolia (denosumab) has not been directly compared to any active treatment, such as intravenous bisphosphonates, for the prevention of skeletal fractures, delay of disease recurrence, or overall survival in patients with early breast cancer.
    - The ABCSG-18 study [17] evaluated the impact of Prolia (denosumab) on disease-free survival (DFS) as a secondary endpoint in women with breast cancer. These results were not reported with the original study publication.

- The intent-to-treat analysis of DFS showed an absolute difference of 1.2% favoring Prolia (denosumab) compared to placebo, and barely met the statistical significance threshold (p = 0.051). [18]
- Subsequently, the 5-year DFS was published, with an absolute difference of 1.9% favoring Prolia (denosumab) compared to placebo, and a DFS of 3.1% at 8 years. As noted in the publication, despite statistical significance, the clinical utility of such a small change in DFS is unknown.[19]
- In the final protocol-defined analysis, at 8 years follow up, the observed difference (1%) in overall survival (OS) between treatment with Prolia (denosumab) compared to placebo was not statistically significant (90.9% vs. 89.9%; HR 0.8; 95% CI 0.64-1.01). [20]

* The NCCN Breast Cancer guideline recommends that women on adjuvant aromatase inhibitor therapy should have monitoring of bone health with a BMD determination at baseline and periodically thereafter. The use of a bisphosphonate is generally the preferred intervention to improve BMD. [21]

Safety

- The most common side effects reported with Prolia (denosumab) include urinary tract infection, upper respiratory tract infection, cataract, constipation, rash, sciatica, and pain in the extremities. [17]
- Both bisphosphonates and Prolia (denosumab) have labeled warnings for risk of osteonecrosis of the jaw (ONJ).
  * ONJ was first reported in patients with advanced cancer receiving high-dose (monthly) bisphosphonate therapy. The incidence of ONJ is much lower with bisphosphonate therapy for osteoporosis (usually annual dosing). [22]
  * When compared to cancer patients receiving antiresorptive treatment, the risk of ONJ for patients with osteoporosis exposed to antiresorptive medications is about 100 times smaller. [23]
  * Based on the current data, the risk of developing ONJ among osteoporotic patients exposed to bisphosphonates or Prolia (denosumab) is real but remains very low. The risk for ONJ among patients treated with either zoledronic acid or Prolia (denosumab) approximates the risk for ONJ of patients enrolled in placebo groups. [23] There is no evidence to establish that Prolia (denosumab) has a lower risk of ONJ, as compared to bisphosphonates (oral or injectable).
  * The risk versus benefit profile should be carefully considered for use of bone resorptive agents [bisphosphonates or Prolia (denosumab)]. Poor baseline health or dental procedures during treatment are known risk factors for ONJ. Thus, patients should be referred for dental evaluation before starting either agent.
- Because of potential safety concerns with long-term use of Prolia (denosumab), it appears to have a less favorable risk versus benefit profile than bisphosphonates for the prevention of osteoporosis.
- Prolia (denosumab) has a new black box warning for an increased risk of severe hypocalcemia in patients with advanced kidney disease. Prolia (denosumab) has a risk

evaluation and mitigation strategy (REMS) in place to ensure that this potential risk is considered before use. [24]

- Prolia (denosumab) contains a warning for an increased risk of fracture following discontinuation of Prolia (denosumab) treatment. Patients who discontinue Prolia (denosumab) should be transitioned to an alternative antiresorptive therapy. Please note that bisphosphonates (including intravenous zoledronic acid) and raloxifene are available without pre-authorization and may be used to transition patients.

Appendix 1: Anabolic Bone medications

Medication	Treatment course
teriparatide (Forteo)	24 months
Evenity (romosozumab)	12 months
Tymlos (abaloparatide)	24 months

Cross References
Bone Density Studies rad2, Medical Policy Manual, TRGMPM – Radiology
Xgeva, denosumab, Medication Policy Manual, Policy No. dru393
Anabolic Bone Medications, Medication Policy Manual, Policy No. dru612

Codes	Number	Description
HCPCS	J0897	Injection, denosumab (Prolia, Xgeva) 1 mg

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24. Prolia [prescribing information]. Thousand Oaks, CA, 91320: March 2024

Revision History

Revision Date	Revision Summary
9/19/2024	• Added additional criterion to define "very high risk" patients (T score ≤ - 3.0). • Removed Bonsity brand name from criteria V.B. (teriparatide is not marketed under this brand name any longer).
9/14/2023	• No criteria changes with this annual review.
9/23/2022	• Reworded criteria for operational clarity (no change to intent). • Added criteria for coverage of "very-high risk of fracture," despite completion of a full course of an anabolic bone medication. • Changed Bonsity to Bonsity/Teriparatide. • Updated benefit coverage to either medical or pharmacy depending on administration status.
10/15/2021	Updated criteria to bypass step therapy requirements for patients at very high risk of fracture (T-score at or below -2.5 and a history of fragility fracture, or multiple fragility fractures).
7/16/2021	Removed Site of Care Program requirement.
10/28/2020	• Added COT criteria. • Revised definition of ineffectiveness for bisphosphonates.
10/23/2019	• No changes to criteria. • Drug holidays addressed in supporting statement.
10/19/2018	Clarified investigational uses.
07/20/2018	• Clarified intent of raloxifene step therapy (ineffective). • Updated criteria with standard policy language (no changes to intent).
8/11/2017	Added raloxifene as an option for step therapy.
3/10/2017	Clarified use in combination with Forteo (teriparatide) is considered investigational.
11/11/2016	Removed site of care language from the individual drug policy; however, requirements still apply. Reference to Site of Care Review, dru408 is provided as part of criterion IA.
10/21/2016	Clarified that both IV and oral bisphosphonates are contraindicated in criterion B.2.c; however, the intent of this criterion has not changed.
3/11/2016	No criteria change.

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Medication Policy Manual | **Policy No:** dru238

Topic: Yervoy, ipilimumab | **Date of Origin:** May 13, 2011

Committee Approval Date: March 6, 2025 | **Next Review Date:** 2025

Effective Date: May 1, 2025

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Yervoy (ipilimumab) is an intravenous immune therapy medication used as a monotherapy or in combination with Opdivo (nivolumab) to treat certain types of cancers.

Policy/Criteria

Most contracts require pre-authorization approval of Yervoy (ipilimumab) prior to coverage.

I. Continuation of therapy (COT):

Yervoy (ipilimumab) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients):

Yervoy (ipilimumab) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) confirming that one of the following criterion A through H below is met.

A. A diagnosis of **melanoma**, **unresectable (stage III) or metastatic (stage IV)**, when Yervoy (ipilimumab) will be given in one of the following two treatment settings (1 or 2):

1. Yervoy (ipilimumab) will be used as monotherapy.

OR

2. For use as combination therapy, both criteria below (a and b) are met:

a. Yervoy (ipilimumab) will be given in combination with Opdivo (nivolumab).

AND

b. No prior therapy with any of the following:
i. Yervoy (ipilimumab).
ii. PD-1/PD-L1 blocking antibody therapy *(see Appendix 1)*.

OR

B. A diagnosis of **melanoma**, **resectable** when criteria 1, 2, and 3 below are met:

1. Documentation of pathologic involvement of regional lymph nodes (stage III).

AND

2. Yervoy (ipilimumab) is used as adjuvant treatment (after complete surgical resection).

AND

3. Yervoy (ipilimumab) will be used as monotherapy.

OR

C. A diagnosis of **colorectal cancer** (CRC), locally advanced or metastatic, when criteria 1 through 4 below are met:

1. The tumor is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) by immunohistochemistry (IHC) or polymerase chain reaction (PCR) testing.

AND

2. There has been disease progression during or after prior therapy with a fluoropyrimidine (e.g., fluorouracil, capecitabine), oxaliplatin, and irinotecan, unless all are not tolerated or there is a documented medical contraindication to each of the three options.

AND

3. No prior therapy with any of the following:
a. Yervoy (ipilimumab).
b. PD-1/PD-L1 blocking antibody therapy *(see Appendix 1)*.

AND

4. Yervoy (ipilimumab) will be used in combination with Opdivo (nivolumab) for a maximum of four doses.

OR

D. A diagnosis of **renal cell carcinoma** (RCC), unresectable locally advanced or metastatic, when criteria 1 through 4 below are met:

1. The disease is considered intermediate- or poor risk (see *Appendix 2*).

AND

2. There has been no prior systemic therapy in the advanced disease setting.

AND

3. No prior therapy with any of the following:
a. Yervoy (ipilimumab).
b. PD-1/PD-L1 blocking antibody therapy *(see Appendix 1)*.

AND

4. Yervoy (ipilimumab) will be used in combination with Opdivo (nivolumab) for a maximum of four doses.

OR

E. A diagnosis of **non-small cell lung cancer** (NSCLC), advanced or metastatic, when criteria 1, 2, and 3 below are met:

1. Yervoy (ipilimumab) is used in combination with Opdivo (nivolumab) AND one of the following applies (a or b):

a. The tumor expresses PD-L1 (≥ 1%).

OR

b. Given in combination with two cycles of platinum-doublet chemotherapy (regardless of PD-L1 status).

AND

2. No prior use of systemic anti-cancer therapy for advanced or metastatic disease (used in the first-line setting).

AND

3. No prior therapy with any of the following:

a. Yervoy (ipilimumab).

b. PD-1/PD-L1 blocking antibody therapy *(see Appendix 1)*.

OR

F. A diagnosis of **hepatocellular carcinoma** (HCC) when criteria 1 through 4 below are met:

1. Confirmation of one of the following (a or b): [provider attestation]

a. Child-Pugh score of 5 to 6 (class A).

OR

b. Child-Pugh Class B AND good performance status (ECOG 0-1)

AND

2. There has been disease progression on, or intolerance to an HCC-active oral tyrosine kinase inhibitor (TKI) [such as sorafenib (generic, Nexavar), or Lenvima (lenvatinib)].

AND

3. Yervoy (ipilimumab) will be used in combination with Opdivo (nivolumab) for a maximum of four doses.

AND

4. No prior therapy with any of the following:

a. Yervoy (ipilimumab).

b. PD-1/PD-L1 blocking antibody therapy *(see Appendix 1)*.

OR

G. A diagnosis of **malignant pleural mesothelioma** (MPM), **unresectable**, when criteria 1, 2, and 3 below are met:

1. No prior use of systemic therapy for advanced disease.

AND

2. Yervoy (ipilimumab) is used in <u>combination</u> with Opdivo (nivolumab).

AND

3. No prior therapy with any of the following:
- **a.** Yervoy (ipilimumab).
- **b.** PD-1/PD-L1 blocking antibody therapy *(see Appendix 1)*.

OR

H. A diagnosis of **esophageal squamous cell carcinoma** (ESCC), unresectable advanced or metastatic, when criteria 1 through 5 below are met:

1. The patient is not a candidate for surgical resection or definitive chemoradiotherapy (CRT).

AND

2. Yervoy (ipilimumab) will be used in combination with Opdivo (nivolumab).

AND

3. The tumor expresses PD-L1 (≥ 1%).

AND

4. Use in the first-line setting, with no prior systemic therapy in the advanced disease setting.

AND

5. No prior therapy with any of the following:
- **a.** Yervoy (ipilimumab).
- **b.** PD-1/PD-L1 blocking antibody therapy *(see Appendix 1)*.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Yervoy (ipilimumab) coverable only under the medical benefit (as a provider-administered medication).

B. When preauthorization is approved, Yervoy (ipilimumab) will be authorized as follows:

1. As monotherapy (melanoma):

Diagnosis	Dosing, as a monotherapy	Duration
Melanoma, resectable (adjuvant)	Up to 10 mg/kg every 3 weeks for four doses, then up to 10 mg/kg every twelve weeks.	Until disease recurrence or for a maximum of 3 years.
Unresectable or metastatic melanoma	Up to 3 mg/kg/dose [up to 600 billing units per claim (600 mg)], for four doses.	***Initial Authorization:*** Up to four infusions (one treatment course), or until disease progression. ***Reauthorization:*** Up to four additional infusions (maximum of one additional treatment course) may be authorized if there is documented disease progression after an initial response to Yervoy followed by at least 3 months of disease stability.

2. Combination therapy with Opdivo (nivolumab) or other medications:

Diagnosis	Dosing, in combination with Opdivo (nivolumab)	Duration
CRC, RCC	Up to 1 mg/kg/dose for four doses with nivolumab (then nivolumab monotherapy).	One-time for a maximum of four infusions (one treatment course), or until disease progression.
HCC, Unresectable or metastatic melanoma	Up to 3 mg/kg/dose for four doses with nivolumab (then nivolumab monotherapy).	
ESCC, NSCLC*, MPM	Up to 1 mg/kg/dose every 6 weeks with nivolumab.	Until disease progression or for a maximum of 2 years (or 24 months).

*In NSCLC Yervoy (ipilimumab) is approved either in combination with Opdivo (nivolumab) alone, or in combination with Opdivo (nivolumab) plus two cycles of chemotherapy. The Yervoy (ipilimumab) dose is the same in either setting.

C. Authorization **may** be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

IV. Yervoy (ipilimumab) is considered investigational when:

A. Infused for more than the dose-maximum listed above (including more than 4 doses for unresectable or metastatic melanoma, CRC, HCC, and RCC).

B. Used in combination with other anticancer medications other than those specifically listed above, including but not limited to other immunotherapies and targeted therapies.

C. Used as a neoadjuvant therapy (prior to surgical excision) for resectable melanoma.

D. Used as adjuvant therapy (after surgical tumor excision) for resectable renal cell carcinoma (RCC).

E. Used for all other conditions, including but not limited to:

1. Breast cancer.

2. Cervical cancer.

3. Leukemia.

4. Non-Hodgkin's lymphoma.

5. Ovarian cancer.

6. Pancreatic cancer.

7. Prostate cancer.

8. Sarcoma.

9. Small cell lung cancer.

10. Urothelial cancer.

Position Statement

- Yervoy (ipilimumab) is a human cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody which is used in the treatment of melanoma, either alone or in combination with Opdivo (nivolumab) for specific cancers.
- The intent of this policy is to cover Yervoy (ipilimumab) in settings where it has been shown to be safe and effective, as detailed in the coverage criteria, with consideration for other available treatment options.
    - * Where there is lack of proven additional benefit and/or lack of demonstrated health outcome (such as overall survival or improved quality of life) relative to alternative therapies, use of Yervoy (ipilimumab) alone or in combination with other therapies is not coverable ("not medically necessary" or "investigational").
    - * It is important to note that the fact that a medication is FDA approved for a specific indication does not, in itself, make the treatment medically reasonable and necessary.
- Many of the clinical indications for immunotherapies (such as CTLA-4, PD-1, PD-L1, and others) have been approved by the FDA and endorsed by clinical guidelines based on surrogate measures such as overall tumor response rate (ORR) and progression-free survival (PFS) which are not proven to accurately predict clinically important outcomes such as improved overall survival or improved quality of life.
- National Comprehensive Cancer Network (NCCN) guidelines recommend Yervoy (ipilimumab) as a potential option in each of the treatment settings listed in the coverage criteria. In general, NCCN recommendations parallel the FDA approved indications.
- Yervoy (ipilimumab) is associated with severe and life-threatening immune-mediated adverse reactions.
- Yervoy (ipilimumab) is given as an intravenous infusion over 30 to 90 minutes. It is covered up to the maximum doses and durations listed in package labeling for the various disease settings for which it is approved, as specified in the coverage criteria.
- Optimal sequencing of chemotherapy and immunotherapy in many cancers is unknown or the data is evolving. At this time, sequential use of immunotherapies is not supported by current evidence. Specifically, there is no evidence to support the sequential use of different CTLA-4, PD-1/PD-L1 inhibitors once there is disease progression on prior CTLA-4 therapy. Therefore, the use of sequential courses of CTLA-4 immunotherapy is not coverable.
- There are ongoing studies using Yervoy (ipilimumab) in a variety of other cancers. However, although initial evidence may be promising, the potential for clinical benefit in these conditions is still being investigated.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.

- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy

Cutaneous Melanoma

- Yervoy (ipilimumab) may be covered for treatment of **advanced malignant cutaneous melanoma** that is unresectable or has metastasized to other areas, a setting where it has been shown to improve overall survival relative to supportive care.

As monotherapy for advanced melanoma

- A large study evaluated the effects of Yervoy (ipilimumab) on overall survival (OS) in patients with previously treated, unresectable, or metastatic melanoma. [1]
    * The triple-arm study included 676 patients with unresectable or metastatic melanoma who had received one or more prior treatments.
    * The study compared Yervoy (ipilimumab) with a gp100 peptide vaccine (an experimental immunotherapy used in the treatment of melanoma). gp100 peptide vaccine has not been shown to impact OS in this population.
    * Yervoy (ipilimumab) was administered in a dose of 3 mg/kg intravenously (IV) every three weeks for a total of 4 doses (one treatment course).
    * Patients in the study who received Yervoy (ipilimumab) had a median OS of approximately 10 months, compared with a reported median OS of 6.4 months in the vaccine-only arm. This is considered a clinically relevant improvement in OS.
    * Limitations to the study included uncertain blinding and concealment of allocation, and uncertainty as to whether the comparator (peptide vaccine) had any positive or negative impact on study patients.
- Yervoy (ipilimumab) has not been compared with any other therapy for unresectable or metastatic melanoma in patients who have had prior medication therapy for melanoma. [2]
- A second study compared Yervoy (ipilimumab) plus dacarbazine versus dacarbazine alone in patients with unresectable or metastatic melanoma who had no prior medication therapy. [3]

* The study reported a median OS advantage of approximately 2 months in the Yervoy (ipilimumab) treatment arm.
* There is low confidence in the results from the trial because of a very high proportion of missing data (~35%) and the potential for confounding due to additional therapies that were used after disease progression.

Combination with Opdivo (nivolumab) for advanced melanoma

- The use of Yervoy (ipilimumab) in combination with Opdivo (nivolumab) was studied in one randomized, double-blind, triple-arm study included 945 patients with unresectable or metastatic melanoma. [4]
  * Patients had not received prior systemic therapy for advanced disease, such as Yervoy (ipilimumab) or a programmed death-1 (PD-1) inhibitor [Opdivo (nivolumab), or Keytruda (pembrolizumab)].
  * Patients were treated with Yervoy (ipilimumab) 3 mg/kg IV along with Opdivo (nivolumab) 1 mg/kg IV every three weeks for four doses, followed by Opdivo (nivolumab) 3 mg/kg IV every two weeks, until disease progression.
  * Combination therapy improved median PFS by approximately 8.5 months relative to monotherapy with either Yervoy (ipilimumab) or Opdivo (nivolumab) [11.5 months versus 2.9 months or 6.9 months, respectively]. The OS data was not yet mature at the time this trial was published.
- There is interest in the use of Yervoy with other PD-1 inhibitors, such as pembrolizumab (Keytruda). however, at this time, there is insufficient evidence to support the use of Yervoy except as noted in the coverage criteria, as either a monotherapy, or in combination with nivolumab (Opdivo). Use in combination with any other PD-1 inhibitor is considered investigational. Yervoy (ipilimumab) has not been studied in combination with Keytruda (pembrolizumab), another PD-1 inhibitor.

Adjuvant therapy for advanced melanoma

- The risk versus the potential benefit of high-dose Yervoy (ipilimumab) as an adjuvant therapy for **resectable cutaneous melanoma** with pathologic involvement of regional lymph nodes (stage III) is unclear. This regimen is poorly tolerated, and it is not known if the toxicities of this therapy outweigh potential clinical benefit.
- A large, randomized, double-blind, trial evaluated Yervoy (ipilimumab) as an adjuvant therapy in subjects with stage III, resectable cutaneous melanoma. [5,6]
  * Subjects were diagnosed with histologically confirmed cutaneous melanoma that was metastatic to the lymph nodes only and had complete excision of the cutaneous lesion with good margins and a complete regional lymphadenectomy. Yervoy (ipilimumab) 10 mg/kg (high-dose) was compared with placebo, each given IV every three weeks for four doses, then every three months for a maximum of three years.
  * At a medium follow-up of 2.7 years, recurrence-free survival (RFS), the primary endpoint, was improved in the Yervoy (ipilimumab) therapy arm relative to placebo (26 months versus 17 months, respectively).

    * In an updated analysis, at a medium follow-up of 5.3 years, the rate of OS was 65.4% in the Yervoy (ipilimumab) group, as compared to 54.4% in the placebo group (hazard ratio for death, 0.72; 95.1% CI, 0.58 to 0.88; P = 0.001).
    * More than half of the subjects withdrew from the Yervoy (ipilimumab) treatment arm due to adverse events versus only 4% in the placebo arm. Immune-related adverse events of any grade occurred in 90% of patients in the Yervoy (ipilimumab) group and 40% of patients in the placebo group. Immune-related adverse events of grade 3 to 5 occurred in 43% of patients in the Yervoy (ipilimumab) treatment group and in 3% of patients in the placebo group. Additionally, five patients in the Yervoy (ipilimumab) arm died due to immune-mediated adverse events attributed to treatment.
- Despite FDA approval, the small change in OS, high toxicity, and poor tolerability of high-dose Yervoy (ipilimumab) observed in this study, it is unclear if the harms of this therapy outweigh any potential clinical benefit when it is used as an adjuvant therapy after complete resection of cutaneous melanoma and regional lymphadenectomy due to pathologic involvement of regional lymph nodes. In addition, there are no studies demonstrating the efficacy of Yervoy (ipilimumab) when used at a lower dose in the adjuvant setting, or whether a potential clinical benefit at a lower dose will outweigh toxicities.

Renal cell carcinoma (RCC)

- Yervoy (ipilimumab) initiated in combination with Opdivo (nivolumab) was approved in **untreated, intermediate- to high-risk, advanced RCC** based on preliminary evidence where it demonstrated a modest improvement in survival at 18 months relative to Sutent (sunitinib). A large, randomized, open-label trial compared the combination of Yervoy (ipilimumab) plus Opdivo (nivolumab) with Sutent (sunitinib) as initial therapy for patients with intermediate- to poor risk, unresectable or metastatic RCC. [7]
    * Yervoy (ipilimumab) was initiated with Opdivo (nivolumab) and was administered for four doses total. Opdivo (nivolumab) was then continued as monotherapy until disease progression.
    * The population included patients of favorable-, intermediate-, or poor-risk disease based on the International Metastatic RCC Database Consortium (IMDC) prognostic model; however, only patients with intermediate- or poor risk disease were evaluated for efficacy.
    * There was no statistical difference in progression-free survival (PFS) between the two treatment groups.
    * There was no difference in radiographic disease progression detected between the two treatment groups. It is too soon to know if the absolute survival difference is clinically relevant as median survival has not been met in either treatment group. An interim analysis at 18 months demonstrated a survival benefit in the Yervoy (ipilimumab) plus Opdivo (nivolumab) treatment arm relative to Sutent (sunitinib) [HR 0.63 (99.8% CI: 0.44, 0.89)]. Median OS has not been reached in either group.

    - Potential areas of bias which may erode the reported survival difference between the therapies include lack of blinding, and a high proportion of subjects who stopped taking study medication who then crossed over to other therapies.
- It is not known how Yervoy (ipilimumab) plus Opdivo (nivolumab) compares with other front-line therapy options. To date this combination has only been compared with Sutent (sunitinib).
- It is too early to determine the overall net health benefit of Yervoy (ipilimumab) plus Opdivo (nivolumab) in advanced RCC.

Hepatocellular carcinoma (HCC)

- Yervoy (ipilimumab) was approved in combination with Opdivo (nivolumab) for advanced HCC after progression of disease on sorafenib based on a small, low-quality study where it was found to shrink the size of tumors in about one out of three patients. A small cohort of patients with advanced HCC who had progressed during or after sorafenib therapy was evaluated in this low-quality, single-arm, open-label, observational trial. [2]
    - Yervoy (ipilimumab) was initiated with Opdivo (nivolumab) and was administered for four doses total. Opdivo (nivolumab) was then continued as monotherapy until disease progression.
    - All patients in the trial had a Child-Pugh class of A5 or A6. Eighty percent had extrahepatic spread of their disease. All enrolled patients had good performance status (ECOG 0-1).
- Sixteen of 49 patients (33%) demonstrated a tumor response during the trial. Only 4 patients (8%) had a complete response. To date there is no evidence that it improves any relevant clinical outcome (e.g., overall survival, quality of life, function, symptom control) in this disease setting.
- The evidence for use of systemic anticancer therapy in Child-Pugh class B HCC is limited to small numbers of patients across pivotal trials. All included patients had good performance status (ECOG 0-1). Additionally, patients with Child-Pugh class C were not included due to their poor performance status. Therefore, coverage of systemic therapies for HCC is limited to patients with good performance status (ECOG 0-1).

Colorectal cancer (CRC)

- Yervoy (ipilimumab) was approved in combination with Opdivo (nivolumab) for patients with mismatch repair deficient (dMMR) or microsatellite stability-high (MSI-H) metastatic CRC based on a small, low-quality, single-arm cohort observational study where it was found to shrink the size of tumors in about one out of two patients. [2]
    - All of the patients enrolled in the trial had disease progression during or after prior treatment with fluoropyrimidine-, oxaliplatin-, or irinotecan-based chemotherapy.
    - Yervoy (ipilimumab) was initiated with Opdivo (nivolumab) and was administered for four doses total. Opdivo (nivolumab) was then continued as monotherapy until disease progression.
    - All patients had microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic disease.

    * Thirty-eight (46%) of 82 patients in the cohort had a tumor response during the trial. Only three patients (3.7%) had a complete response.

- To date there is no evidence that it improves any relevant clinical outcome (e.g., overall survival, quality of life, function, symptom control) in this disease setting.

Non-small cell lung cancer (NSCLC)

- Yervoy (ipilimumab) was approved in combination with Opdivo (nivolumab) as a front-line therapy for patients with recurrent or metastatic NSCLC two different settings, based on improved overall survival relative to platin-doublet chemotherapy:
    * In patients with no known EGFR mutations or ALK translocations, regardless of PD-L1 status when given with two cycles of platin-doublet chemotherapy.
    * In patients with no known EGFR mutations or ALK translocations, but whose tumors expressed PD-L1 (≥ 1%).
- Approval of Yervoy (ipilimumab) in combination with Opdivo (nivolumab) as a front-line therapy in patients with metastatic NSCLC expressing PD-L1 (≥ 1%) is based on an open-label trial that compared this immunotherapy regimen with platin-doublet chemotherapy. [2,8]
    * Patients had no known EGFR mutations or ALK translocations.
    * Patients were given Yervoy (ipilimumab) every 6 weeks plus Opdivo (nivolumab) every 2 weeks until disease progression, or up to two years in patients without disease progression.
    * The median OS was 17.1 months [95% CI: 15.0, 20.1] and 14.9 months [95% CI: 12.7, 16.7] in the Yervoy (ipilimumab) plus Opdivo (nivolumab) and platinum-doublet chemotherapy treatment arms, respectively.
- Approval of Yervoy (ipilimumab) in combination with Opdivo (nivolumab) as a front-line therapy in patients with metastatic NSCLC regardless of PD-L1 status is based on an open-label trial that compared this immunotherapy regimen plus two cycles of platin-based chemotherapy with standard platin-doublet chemotherapy. [2]
    * To be enrolled in the trial, patients could have no known EGFR mutations or ALK translocations.
    * Patients were given Yervoy (ipilimumab) every 6 weeks plus Opdivo (nivolumab) every 3 weeks in combination with two cycles of a platinum-doublet until disease progression, or up to two years in patients without disease progression.
    * The median OS was 14.1 months [95% CI: 13.2, 16.2] and 10.7 months [95% CI: 9.5, 12.5] in the Yervoy (ipilimumab) plus Opdivo (nivolumab) plus platin-doublet chemotherapy, and platinum-doublet chemotherapy treatment arms, respectively.

Malignant pleural mesothelioma (MPM)

- Yervoy (ipilimumab) was approved in combination with Opdivo (nivolumab) as a front-line therapy for patients with unresectable MPM based on a large, open-label randomized controlled trial (RCT) that demonstrated a four-month improvement in median OS relative to platinum-based chemotherapy, the standard of care. [9]
    * Patients were given Yervoy (ipilimumab) every 6 weeks [in combination with Opdivo (nivolumab)] until disease progression, or up to two years in patients without disease

progression.

* The median OS was 18.1 months and 14.1 months in the Yervoy (ipilimumab)/ Opdivo (nivolumab) and chemotherapy treatment arms, respectively [HR 0.74 (95% CI 0.61, 0.89); p = 0.002].

Esophageal Squamous Cell Carcinoma (ESCC)

- Yervoy (ipilimumab) was approved in combination with Opdivo (nivolumab) as a potential front-line therapy for unresectable advanced or metastatic ESCC based on a large randomized, open-label trial that demonstrated a 2-month improvement in median OS relative to standard front-line chemotherapy. [10] This is likely an overestimate of expected survival benefit in the general population due to the following:
  * The trial was enriched with patients whose tumors overexpressed PD-L1 (PD-L1 ≥ 1%) and were therefore more likely to respond to this immunotherapy combination. Subgroup analyses support this analysis as there was a 4.5-month improvement in median OS relative to standard chemotherapy in the PD-L1 ≥ 1% population; however, there was no survival benefit relative to chemotherapy in the PD-L1 < 1% population. *(Note: Forty-nine percent of the study population had PD-L1 expression ≥ 1%)*
  * Only 16% of patients in the chemotherapy arm received a PD-(L)1 inhibitor after disease progression. Follow-on therapy with a PD-(L)1 inhibitor is standard of care in the US based on current guidelines. There are currently two PD-1 inhibitors approved as monotherapy in the US for ESCC in the second-line setting (after progression on chemotherapy).
- Optimal sequencing of therapies in ESCC has not yet been determined.

CLINICAL GUIDELINES

- The National Comprehensive Cancer Network (NCCN) melanoma guideline lists Yervoy (ipilimumab), and Yervoy (ipilimumab) plus Opdivo (nivolumab) as a category 2A recommendation as a second-line or subsequent therapy in patients with or without BRAF V600 mutation positive melanoma. The use of Yervoy (ipilimumab) in combination with Opdivo (nivolumab) is a category 1 recommendation in the first-line metastatic setting.
- The NCCN gives high-dose Yervoy (ipilimumab) a category 2A recommendation in the adjuvant treatment of stage III cutaneous melanoma where it may have use when there has been prior exposure to anti-PD-1 therapy. [11]
- The NCCN melanoma guideline includes a footnote indicating that re-induction with Yervoy (ipilimumab) may be considered for select patients who experienced no significant systemic toxicity during prior therapy and who relapse after initial clinical response or progress after stable disease. [11,12]

For other cancers, the NCCN guideline lists the following: [11]

- The combination of Yervoy (ipilimumab) plus Opdivo (nivolumab) among preferred treatment options for first-line intermediate- to poor-risk, unresectable or metastatic RCC. It is a category 2A recommendation for low-risk disease.
- Yervoy (ipilimumab) in combination with Opdivo (nivolumab) as a treatment option for microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic

CRC when disease has progressed after FOLFOX or CAPEOX.

- Yervoy (ipilimumab) in combination with Opdivo (nivolumab) as a treatment option as a subsequent-line therapy for HCC.
- The combination of Yervoy (ipilimumab) and Opdivo (nivolumab) among preferred, front-line regimens for MPM.
- Yervoy (ipilimumab) in combination with Opdivo (nivolumab) as a treatment option 'useful in certain circumstances' when the tumor expresses PD-L1. It is also listed as a category 2A 'other' recommendation as an initial therapy for metastatic NSCLC that does not express PD-L1.
- Yervoy (ipilimumab) plus Opdivo (nivolumab) is listed as a category 2A recommendation among many potential front-line regimens for advanced ESCC. The guideline notes that use should be limited to cases where there has been no tumor progression with prior checkpoint inhibitor therapy.

INVESTIGATIONAL USES

- Data to support the use of combination treatment with Yervoy (ipilimumab) and Opdivo (nivolumab) for the treatment of small cell lung cancer (SCLC) is limited to a single phase I/II trial. Response rates were reported with the combination treatment in SCLC after primary therapy, but not overall survival. Combination treatment with Yervoy (ipilimumab) and Opdivo (nivolumab) have not been shown to be superior to many available alternative therapies in patients with SCLC. Larger, well-designed, randomized, controlled trials are needed to confirm preliminary results. [13]
- Yervoy (ipilimumab) demonstrated some antitumor activity in small trials in patients with non-Hodgkin Lymphoma, and sarcoma. Larger, well-controlled clinical trials in these settings are needed to confirm clinical benefit. [14-16]
- Yervoy (ipilimumab) failed to demonstrate any clinical benefit in castration-resistant prostate cancer (as monotherapy) and small cell lung cancer (in combination with cytotoxic chemotherapy) in two large, phase 3 trials. [17,18]
- There is interest in using Yervoy (ipilimumab) in the neoadjuvant melanoma setting; however, evidence to date is preliminary and hypothesis generating. A phase 3 randomized, comparative trial is needed to determine if neoadjuvant therapy confers any additional benefit over standard current therapies (e.g., adjuvant immunotherapies).
- A randomized, double-blind, placebo-controlled trial (CheckMate 914) evaluated the combination of Opdivo (nivolumab) and Yervoy (ipilimumab) as an adjuvant therapy for patients with resectable renal cell carcinoma (RCC) who were at high risk of relapse. No difference in relapse-free survival (RFS) was detected between the treatment and placebo groups. The number of deaths was similar in each treatment arm; however, OS data is not yet mature. [19]

Safety

- The most common adverse effects (AEs) reported with Yervoy (ipilimumab) include fatigue, diarrhea, pruritus, rash, and colitis. Additional common AEs observed at the higher, 10 mg/kg dose, include nausea, vomiting, headache, weight loss, pyrexia, decreased appetite, and insomnia. Yervoy (ipilimumab) carries a boxed warning for severe immune-

mediated adverse reactions including immune-mediated hepatitis and endocrinopathies. For severe reactions, the prescribing information recommends Yervoy (ipilimumab) be permanently discontinued. For moderate reactions, the prescribing information states the dose of Yervoy (ipilimumab) should not be given and systemic corticosteroids are recommended. [2]

Dosing Considerations

- Dosing and administration vary based on the setting in which Yervoy (ipilimumab) is used. Consult package labeling for details. [2]
- High-dose (10 mg/kg IV every three weeks) Yervoy (ipilimumab), which is approved for adjuvant use in patients with stage 3 melanoma, is poorly tolerated. [12]
- The evidence for retreatment with ipilimumab when there is disease progression after initial response in patients with advanced melanoma is based on low-quality evidence. [12,20,21]
    * Patients in these observational studies were retreated with up to an additional four doses (one treatment course) of ipilimumab after disease progression.
    * Approximately half were able to achieve a temporary response to the additional treatment course. Most of the responders achieved stable disease; however, some patients had a partial response, and a few had a complete response.
    * It is not known if retreatment improves any clinical outcome such as improved survival or quality of life.

Appendices

Appendix 1:

FDA- approved PD-1 and PD-L1 blocking monoclonal antibody therapies [a]
Programmed death receptor-1 (PD-1) inhibitors
Jemperli (dostarlimab)
Keytruda (pembrolizumab)
Libtayo (cemiplimab-rwlc)
Loqtorzi (toripalimab)
Opdivo (nivolumab), Opdivo Qvantig (nivolumab-hyaluronidase-nvhy)
Tevimbra (tislelizumab)
Zynyz (retifanlimab)
Programmed death-ligand 1 (PD-L1) inhibitor
Bavencio (avelumab)
Imfinzi (durvalumab)
Tecentriq (atezolizumab), Tecentriq Hybreza (atezolizumab- hyaluronidase-tqjs)

[a] Or as listed on the FDA.gov website. Several PD-1s are in the drug development pipeline. This is a list of the PD-1 inhibitors FDA-approved in the US at the time this policy was approved.

Appendix 2:

International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) Prognostic Model [7]

Number of Risk Factors	Expected Outcome
0	Low risk, with good prognosis
1 or 2	Intermediate risk
3 or more	Poor risk

Risk factors: *(predicators of shortened survival)*

- Serum hemoglobin < lower limit of normal
- Corrected serum calcium > upper limit of normal
- Karnofsky performance status score < 80% (not capable of caring for self, or normal activity or work)
- Time from initial diagnosis to initiation of treatment of < 1 year
- Absolute neutrophil count > upper limit of normal
- Platelets > upper limit of normal

Cross References
BRAF inhibitors, Medication Policy Manual, Policy No. dru728
Imlygic, talimogene laherparepvec, Medication Policy Manual, Policy No. dru445
Mitogen-activated extracellular signal-regulated kinase (MEK) Inhibitors, Medication Policy Manual, Policy No. dru727
PD-1 and PD-L1 Inhibitor Monoclonal Antibody Therapies, Medication Policy Manual, Policy No. dru797
Lenvima, lenvatinib, Medication Policy Manual, Policy No. dru398

Codes	Number	Description
HCPCS	J9228	Injection, ipilimumab (Yervoy), 1 mg

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Revision History

Revision Date	Revision Summary
3/6/2025	Updated coverage criteria for hepatocellular carcinoma to include Child-Pugh B with good performance status (ECOG 0-1).
6/20/2024	No changes to coverage criteria with this annual review.
12/7/2023	Fixed typo in criterion E1. No change to intent of policy.
9/14/2023	• Clarification of criteria wording to align with associated policies. Specifically, indications in which Yervoy (ipilimumab) is used in combination with Opdivo (nivolumab), no change to intent. • Adjuvant use of Yervoy (ipilimumab) in resectable renal cell carcinoma (RCC) was added as investigational based on a failed phase 3 study in this setting.
9/23/2022	• Added coverage criteria for Yervoy (ipilimumab) as a combination therapy with Opdivo (nivolumab) for first-line treatment of ESCC based on new evidence and a new FDA indication. • Added quantity limits for Yervoy (ipilimumab) when used in ESCC. • Added neoadjuvant (prior to surgical resection) use of Yervoy (ipilimumab), either alone or in combination with other medications, as investigational. There is insufficient evidence to support this use currently.
10/15/2021	No changes to coverage criteria with this annual update.
7/16/2021	Updated criteria and quantity limits for advanced melanoma to allow for one additional treatment course (up to four additional ipilimumab infusions) in cases where disease has advanced three or more months after response to initial treatment.
4/21/2021	• Added coverage criteria for malignant pleural mesothelioma. • Clarification of criteria wording to align with associated policies (no change to intent). • Updated the QLL language to include HCC and MPM. • Updated 'Investigational uses' (added HCC to the indications list for more than 4 doses as being investigational. This was an oversight from a previous update).
10/28/2020	No changes to coverage criteria with this annual update.
7/22/2020	• Added coverage criteria for use in advanced hepatocellular carcinoma. • Added coverage criteria for use in front-line metastatic NSCLC. • Updated quantity limitations for new indications. • Updated 'Investigational uses' (removed NSCLC).
10/23/2019	Kidney cancer (renal cell carcinoma) was removed from the list of 'Investigational' conditions (oversight from prior update). No other changes to criteria or intent.

Revision Date	Revision Summary
8/17/2018	• Added coverage criteria for use in advanced RCC and metastatic CRC. • Updated the list of 'investigational uses' (added SCLC). • Updated the 'Administration, Quantity Limitations, and Authorization Period' section to include the new indications and clarified duration of coverage for use in adjuvant melanoma.
10/13/2017	Added coverage criteria for adjuvant use in resectable cutaneous melanoma when there is pathologic involvement of regional lymph nodes (stage III).
5/13/2016	• Added adjuvant use of high-dose (10 mg/kg) Yervoy (ipilimumab) for resectable cutaneous melanoma when there is pathologic regional lymph node involvement as not medically necessary. This is a newly approved FDA-labeled use. • Updated guideline recommendations, added newly published evidence, and updated Appendices.
12/11/2015	• Added policy coverage criteria for the use in combination with Opdivo. • Clarified that dose is 3 mg/kg. • Add Appendix 1, with a list of available PD1s. • Add Appendix 3, with a list of other targeted therapies for melanoma.

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Medication Policy Manual | **Policy No:** dru264

Topic: Adcetris, brentuximab vedotin | **Date of Origin:** November 11, 2011

Committee Approval Date: March 6, 2025 | **Next Review Date:** 2026

Effective Date: May 1, 2025

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Adcetris (brentuximab vedotin) is an intravenously administered medication used in the treatment of certain lymphomas (Hodgkin lymphoma and several types of rare non-Hodgkin lymphomas).

Policy/Criteria

Most contracts require pre-authorization approval of Adcetris (brentuximab vedotin) prior to coverage.

I. Continuation of therapy (COT): Adcetris (brentuximab vedotin) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Adcetris (brentuximab vedotin) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that one of the following criterion A, B, C, or D below is met:

A. A diagnosis of **classical Hodgkin lymphoma** (cHL) when at least one of the criteria 1, 2, or 3 below are met:

1. A diagnosis of previously untreated cHL and both criteria below (a and b) are met:

a. One of the following criteria (i or ii) below are met:

i. Advanced stage cHL (stage III or IV)

OR

ii. High-risk cHL, defined as stage IIB with bulk disease, stage IIIB, stage IVA, or stage IVB.

AND

b. Both of the following criteria (i and ii) below are met:

i. The patient has not received prior chemotherapy or radiotherapy.

AND

ii. Adcetris (brentuximab vedotin) will be administered with cytotoxic chemotherapy, such as AVD (doxorubicin, vinblastine, and dacarbazine) or AVE-PC (doxorubicin, vincristine, etoposide, prednisone, and cyclophosphamide).

OR

2. A diagnosis of relapsed/refractory cHL, as defined by one of the following criterion (a or b) below:

a. An autologous stem cell transplant (ASCT) for cHL has not been successful.

OR

b. A minimum of two prior multi-agent chemotherapy regimens for cHL were not effective or were not tolerated.

OR

3. Adcetris (brentuximab vedotin) will be used as post-ASCT consolidation therapy for cHL AND the patient is at high risk of relapse or progression as defined by one of the following three high-risk categories (a, b, or c):

a. Primary refractory cHL (i.e., failure to achieve complete remission following initial frontline therapy).

OR

b. Relapsed cHL with an initial remission duration of less than 12 months.

OR

c. Presence of extranodal involvement (e.g., chest wall, bone, lung, liver).

OR

B. A diagnosis of one of the following subtypes of **CD30-expressing peripheral T-cell lymphoma** (PTCL):

1. Systemic anaplastic large cell lymphoma (sALCL).

2. Peripheral T-cell lymphoma (PTCL), not otherwise specified (NOS).

3. Angioimmunoblastic T-cell lymphoma (AITL).

OR

C. A diagnosis of **primary cutaneous anaplastic large cell lymphoma** (pcALCL) with multifocal lesions.

OR

D. A diagnosis of **CD30-expressing mycosis fungoides (MF)** when at least one prior systemic therapy has not been effective or was not tolerated.

III. Administration, Quantity Limitations, and Authorization Period:

A. Regence Pharmacy Services considers Adcetris (brentuximab vedotin) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Adcetris (brentuximab vedotin) will be authorized in the following quantities:

1. Classical Hodgkin lymphoma (cHL):

a. ***Previously untreated high-risk or advanced stage:***

i. Adult: Doses up to 120 mg every two weeks for a treatment course of up to 12 infusions.

ii. Pediatric: Doses up to 180 mg every three weeks for a treatment course of up to 5 infusions.

b. ***Consolidation (post ASCT):*** Doses up to 180 mg every three weeks for a treatment course of up to 16 infusions

c. ***Relapsed/refractory disease:*** Doses up to 180 mg every three weeks until disease progression.

2. For the following subtypes of CD30-expressing peripheral T-cell lymphoma: sALCL, PTCL NOS, and AITL:

a. ***Previously untreated disease:*** Doses up to a maximum of 180 mg every three weeks for a treatment course of up to 8 infusions.

b. ***Relapsed disease:*** Doses up to 180 mg every three weeks until disease progression.

3. Primary cutaneous anaplastic large cell lymphoma (pcALCL): Doses up to 180 mg every three weeks for a treatment course of up to 16 infusions.

4. CD30-expressing mycoses fungoides (MF): Doses up to 180 mg every three weeks for a treatment course of up to 16 infusions.

C. Authorization period:

1. Classical Hodgkin lymphoma (cHL):

a. ***Previously untreated stage III or IV, and consolidation (post ASCT):*** No additional doses beyond the maximum number of doses stated above will be authorized.

b. ***Relapsed/refractory disease:*** Authorization **may** be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

2. **For the following subtypes of CD30-expressing peripheral T-cell lymphoma: sALCL, PTCL NOS, and AITL:**
   a. ***Previously untreated disease:*** No additional doses beyond the maximum number of doses stated above will be authorized.
   b. ***Relapsed disease:*** Authorization **may** be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.
3. **Primary cutaneous anaplastic large cell lymphoma (pcALCL):** No additional doses beyond the maximum number of doses stated above will be authorized.
4. **CD30-expressing mycoses fungoides (MF):** No additional doses beyond the maximum number of doses stated above will be authorized.

IV. Use of Adcetris (brentuximab vedotin) beyond one treatment course, as defined above is considered investigational. Additionally, Adcetris (brentuximab vedotin) is considered investigational when used for all other conditions.

Position Statement

- Adcetris (brentuximab vedotin) is a medication that combines the action of an antibody with chemotherapy (an antibody-drug conjugate). It is directed against CD30, a cell membrane protein associated with certain types of lymphoma.
- Adcetris (brentuximab vedotin) is approved for use in several classical Hodgkin lymphoma (cHL) settings, relapsed systemic anaplastic large cell lymphoma (sALCL), and relapsed primary cutaneous anaplastic large cell lymphoma (pcALCL) or CD30-expressing mycosis fungoides (MF). It is given via intravenous infusion over 30 minutes.
- In cHL, Adcetris (brentuximab vedotin) has been studied in the following populations:
  * In patients with advanced or high-risk (stage IIB, III, or IV) disease as an initial therapy when given as a component of a chemotherapy regimen.
  * As consolidation therapy following autologous stem cell transplant (ASCT) in the following high-risk patient populations: those with primary refractory Hodgkin's lymphoma (failure to achieve complete remission), relapsed Hodgkin's lymphoma with an initial remission duration of less than 12 months, or extranodal involvement at the start of pre-transplantation salvage chemotherapy.
  * In patients with relapsed or refractory cHL who received a median of five prior therapies including ASCT.
- Several clinical trials have also evaluated Adcetris (brentuximab vedotin) in rare subtypes of CD30-expressing non-Hodgkin lymphomas, including systemic anaplastic large cell lymphoma (sALCL), primary cutaneous anaplastic large cell lymphoma (pcALCL), angioimmunoblastic T-cell lymphoma (AITL), peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), and relapsed mycoses fungoides (MF).

- The evidence for Adcetris (brentuximab vedotin) is generally of low quality. Efficacy is based on response rates and progression-free survival. These surrogate endpoints have not been shown to correlate with improved survival or quality of life.
- The NCCN ***Hodgkin lymphoma*** guideline lists Adcetris (brentuximab vedotin) as a potential therapy for most of its labeled indications.
- The NCCN ***T-cell lymphomas*** guideline lists Adcetris (brentuximab vedotin) as the sole preferred, category 1 recommendation for primary treatment of pcALCL with multifocal lesions. It is listed among recommended options for other rare, CD30-expressing non-Hodgkin lymphomas including PTCL-NOS, AITL, relapsed ALCL, and relapsed MF.
- The most common adverse effects reported with Adcetris (brentuximab vedotin) include bone marrow depression, severe peripheral sensory neuropathy, infusion reactions, and risk of infection were reported in clinical trials. Peripheral neuropathy may persist after Adcetris (brentuximab vedotin) is discontinued.
- There is no evidence to support more than one treatment course of Adcetris (brentuximab vedotin), or continuation of therapy after disease progression. In addition, use of Adcetris (brentuximab vedotin) multiple disease settings within the same patient has not been studied. For example, if a patient receives a treatment course in the front-line setting, its use in a subsequent treatment setting (e.g., after relapse) has not been studied.
- There is interest in using Adcetris (brentuximab vedotin) in other types of cancers where CD30 may be expressed as well as in additional cHL settings; however, there is currently not sufficient evidence to support coverage outside of the clinical settings listed above.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy

CLASSICAL HODGKIN LYMPHOMA (cHL)

Relapsed/refractory cHL after ASCT:

- A phase 2, single-arm trial evaluated the efficacy of Adcetris (brentuximab vedotin) in 102 subjects with Hodgkin lymphoma that was refractory to or relapsed following autologous stem cell transplantation (ASCT). [1]
    * The study reported overall response rates of 75% in this population.
    * Overall response rates have not been correlated with clinically meaningful outcomes (e.g., overall survival, quality of life) in this condition.
- It is not known how Adcetris (brentuximab vedotin) compares with cytotoxic chemotherapy in the treatment of relapsed/refractory Hodgkin Lymphoma. There is no evidence that compares Adcetris (brentuximab vedotin) with any other therapy in this setting, including best supportive care.
- The National Comprehensive Cancer Network (NCCN) guideline for Hodgkin lymphoma lists Adcetris (brentuximab vedotin) as an option for patients with relapsed or refractory disease (after a failed ASCT or when at least two prior multi-agent chemo-therapy regimens have not been effective). Several multi-agent chemotherapy regimens are also listed as recommended treatment options (see *Appendix 1*). [2]

As consolidation therapy after ASCT:

- A published, phase 3 randomized controlled trial in 329 patients evaluated the efficacy of Adcetris (brentuximab vedotin) versus placebo as a consolidation therapy following ASCT in patients with Hodgkin lymphoma at high risk for relapse or progression. [3]
    * Patients considered being at high risk for relapse or progression included patients with primary refractory primary refractory Hodgkin's lymphoma (failure to achieve complete remission), relapsed Hodgkin's lymphoma with initial remission duration of less than 12 months, or extranodal involvement at the start of pre-transplantation salvage chemotherapy.
    * The primary endpoint was progression-free survival (PFS), with secondary endpoints focused on overall survival (OS) and safety.
    * The majority (60%) of patients in the trial were refractory to frontline therapy and all patients were required to have obtained a complete remission (CR), partial remission (PR), or stable disease (SD) to salvage therapy prior to ASCT.
    * The median PFS with Adcetris (brentuximab vedotin) was 42.9 months compared to 24.1 months for placebo.
    * At the time of the interim analysis, there was no statistically significant difference in OS between groups. This endpoint was potentially confounded by crossover, as 85% of patients in the placebo arm received Adcetris (brentuximab vedotin) when the trial was unblinded.
    * PFS has not been correlated with clinically meaningful outcomes (e.g., overall survival, quality of life) in this condition.
- NCCN lists Adcetris (brentuximab vedotin) as an option for consolidation therapy following ASCT in patients at high risk for relapse or progression. Several multi-agent chemotherapy regimens are also listed as recommended treatment options (see *Appendix 1*). [2]

Previously untreated cHL (first-line):

- A large, open-label RCT (ECHELON-1) compared standard chemotherapy (ABVD; doxorubicin, bleomycin, vinblastine, and dacarbazine) with Adcetris (brentuximab vedotin) plus chemotherapy (A-AVD; as above minus bleomycin) in adult patients with previously untreated, advanced stage (stage III or IV) cHL. [4]
    * In an initial assessment, the 2-year PFS (independent assessors) was reported as 77.2% and 82.1%, respectively. There was no statistically significant OS difference noted (2-year OS of 94.9% vs 96.6%, respectively; p = NS).
    * Subsequently, a 6-year follow-up reported overall survival estimates of 93.9% with A-AVD and 89.4% with ABVD [HR 0.59; (95% CI: 0.40, 0.88); p=0.009]. [5]
    * The relative survival advantage for A-AVD is not robust as there may have been confounding factors that impacted the results such as differences in follow-on therapies. Median OS data is not yet mature.
    * A significant increase in fever and neutropenia, some cases of which were fatal, was reported in the Adcetris (brentuximab vedotin) treatment arm.
    * Approximately 1.5% of subjects in the ABVD arm died of pulmonary toxicity; the ECHELON-1 trial did not utilize PET-adjusted chemotherapy nor did the protocol specify regular monitoring of study subjects for pulmonary toxicity. The magnitude of the benefit associated with Adcetris (brentuximab vedotin) compared to current standards of care in the US is not clear.
    * Subgroup analyses showed inconsistent benefit. There was no OS benefit in subjects with lower risk (Stage III or IPS 0-1) disease; it is unclear if Adcetris (brentuximab vedotin) is potentially inferior to PET-adjusted ABVD in these patients.
- NCCN guidelines for adult Hodgkin lymphoma recommend PET-adjusted ABVD or A-AVD (if neuropathy not present) as potential treatment options in the first line setting. Adcetris (brentuximab vedotin) has not been compared to PET-adjusted chemotherapy such as ABVD followed by AVD for patients with Deauville 1-3 or eBEACOPP for patients with Deauville 4-5. The comparative efficacy of Adcetris (brentuximab vedotin) + AVD to PET-adjusted chemotherapy with ABVD is not known.[2]
- Subsequently, a large, open-label, active-control RCT (AHOD1331) compared standard chemotherapy (ABVE-PC; doxorubicin, bleomycin, vinblastine, etoposide, prednisone, and cyclophosphamide) with Adcetris (brentuximab vedotin) plus chemotherapy (Bv-AVEPC; as above minus bleomycin) in pediatric patients with previously untreated, high-risk cHL (n=600). [6]
    * High-risk was defined as Ann Arbor Stage IIB with bulk disease, Stage IIIB, Stage IVA, and Stage IVB.
    * The primary endpoint of event free survival (EFS) was 92.1% with Bv-AVEPC vs. 82.5% ABVE-PC (p<0.001).
    * Secondary safety and overall survival (OS) endpoints were not statistically significantly different between the groups. Subjects had similar use of radiation therapy, and same frequency of toxicities. OS at 3 years was 99.3% (95% CI, 97.3 to 99.8) with Bv-AVEPC vs 98.5% (95% CI, 96.0 to 99.4) with ABVE-PC.

- NCCN guidelines for pediatric Hodgkin lymphoma list PET-adjusted regimens of Bv-AVEPC and OEPA (vinblastine, etoposide, prednisone, and doxorubicin) as preferred (category 1) treatment options in the first line setting for high-risk disease. Both regimens have FDG-PET response-based use of ISRT, modified based on response to initial cycles of chemotherapy. The comparative efficacy of Adcetris (brentuximab vedotin) + AVEPC to OEPA is not known.[2]

OTHER cHL TREATMENT SETTINGS

- There is interest in using Adcetris (brentuximab vedotin) as a front-line option in older patients (> 60 years of age) with Hodgkin lymphoma who may be unable to tolerate conventional combination chemotherapy. Although initial findings appear promising, larger, well-controlled trials are needed to confirm the results. [7]
- The NCCN Hodgkin lymphoma guideline lists Adcetris (brentuximab vedotin) among a list of several potential second-line therapies for relapsed or refractory cHL. The evidence for use earlier in therapy is based on small, non-comparative (single-arm) trials that report overall response rates (ORR) as a surrogate endpoint.
    * A small, single-arm study conducted by Younis, et al. evaluated ORR in patients who received Adcetris (brentuximab vedotin) monotherapy for confirmed CD30-positive cHL who had relapsed or refractory disease after an autologous stem cell transplant (auto-SCT). The number of prior therapies (excluding the auto-SCT) ranged from one to thirteen, with a median of 3.5. Forty-two percent of patients had disease that was refractory to the most recent cHL therapy. The ORR in this study was reported as 75%. [8]
    * A second, small, single-arm, phase 1/2, multi-cohort study conducted by O'Connor, et al. evaluated safety (primary endpoint) and ORR (secondary endpoint) in patients with CD30-positive relapsed or refractory cHL. Thirty-seven patients entered the phase 2 (efficacy) portion of the study and received a combination of Adcetris (brentuximab vedotin) and bendamustine. Patients had at least one prior cHL therapy, with no upper limit for the total number of prior therapies. The median number of prior therapies was not reported; however, the population was described as being heavily pretreated and 78% of the population was reported to have received prior platinum-based therapy in the second- or subsequent-line setting. The ORR in this study was reported as 78%. [9]
- There is also interest in using Adcetris (brentuximab vedotin) for cHL in combination with Opdivo (nivolumab). Available published evidence is based on two, small, single-arm, observational trials.
    * Preliminary results from a study of 60 patients with relapsed or refractory cHL suggest complete remission rates that are similar to complete remission rates reported with second-line salvage chemotherapy. The durability of effect with this combination is not yet known. [10]
    * A second study in 46 previously untreated patients with cHL with a mean age of 71.5 years and who were considered unsuitable for standard chemotherapy (ABVD) was closed early because it did not meet predefined efficacy parameters. [11]

CD30-EXPRESSING PERIPHERAL T-CELL LYMPHOMAS (PTCL)

- A multicenter, double-blind RCT [ECHELON-2 study] evaluated Adcetris (brentuximab vedotin) in patients with several subtypes of CD30-expressing peripheral T-cell lymphomas (PTCLs). [12,13]
  * The trial compared the addition of Adcetris (brentuximab vedotin) to a backbone regimen of CHOP chemotherapy, to CHOP chemotherapy plus placebo.
  * Subjects enrolled in the trial had CD30-expresssion of at least 10% per immuno-histochemistry.
  * The trial included the following subtypes of PTCL:
    - Systemic anaplastic large cell lymphoma (sALCL) [70%]
    - PTCL, not otherwise specified [16%]
    - Angioimmunoblastic T-cell lymphoma [12%]
    - Adult T-cell leukemia/lymphoma [2%]
    - Enteropathy-associated T-cell lymphoma [< 1%]
  * The efficacy was driven by the population with sALCL. There were too few subjects with adult T-cell leukemia/lymphoma and enteropathy-associated T-cell lymphoma to draw any conclusions regarding potential efficacy.
  * This trial excluded subjects with primary cutaneous ALCL (pcALCL).
  * Median PFS, the primary endpoint, was significantly longer in the brentuximab vedotin (Adcetris) versus the placebo arm of the trial. Median OS has not been reached in either treatment arm.
- A phase 2, single-arm trial evaluated the efficacy of Adcetris (brentuximab vedotin) in 58 subjects with systemic ALCL that was refractory to or relapsed following at least one multi-agent chemotherapy regimen. [14]
  * The study reported overall response rates of 86% in this population.
  * Overall response rates have not been correlated with clinically meaningful outcomes (e.g., overall survival, quality of life) in this condition.
- The NCCN ***T-cell lymphomas*** guideline lists Adcetris (brentuximab vedotin) among several recommended treatment options for certain rare, CD30-expressing non-Hodgkin lymphomas including PTCL-NOS, AITL, and relapsed ALCL. [2]

PRIMARY CUTANEOUS ALCL AND CD30-EXPRESSING MYCOSIS FUNGOIDES

- A small, open-label RCT compared Adcetris (brentuximab vedotin) with physician's choice of methotrexate or Targretin (bexarotene) in patients with either primary cutaneous anaplastic large cell lymphoma (pcALCL) or CD30-expressing mycosis fungoides (MF). [12]
  * Patients enrolled in the trial had relapsed or refractory disease with a median of two prior systemic therapies.
  * The therapies were evaluated based on their ability to achieve an objective response that lasted at least 4 months (ORR4). Patients in the Adcetris (brentuximab vedotin) and physician's choice of therapy arms had on ORR4 of 56.3% and 12.5%, respectively.

    * ORR4 is a surrogate endpoint and has not been shown to predict improvement in survival in clinically relevant outcomes, such as OS and quality of life.
- The NCCN T-cell lymphomas guideline lists Adcetris (brentuximab vedotin) as a preferred regimen (category 1) for pcALCL when multifocal lesions are present. [2] It is listed among potential recommended treatment options for CD30-expressing MF. [2]

USE IN OTHER CONDITIONS

- A small, phase 1/2, observational trial evaluated tumor response rates in a mixed population of 29 subjects with various CD30-positive B-cell lymphomas. [15]
    * Patients in the trial were given six cycles of Adcetris (brentuximab vedotin) in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone.
    * The population included 22 subjects with primary mediastinal B-cell lymphoma (PMBCL), 5 subjects with diffuse large B-cell lymphoma (DLBCL), and 2 subjects with gray zone lymphoma (GZL).
    * Consolidative radiation was used in 52% of the subjects.
    * The trial is of low quality due to the small number of subjects, the heterogeneous population, and the lack of control (no comparator, randomization, or blinding).
- The net health benefit of Adcetris (brentuximab vedotin) outside of the clinical settings described in the coverage criteria has not been confirmed.

Safety [1,12]

- The most commonly reported adverse events with Adcetris (brentuximab vedotin) in clinical trials included neutropenia, peripheral sensory neuropathy, fatigue, nausea, anemia, upper respiratory tract infection, diarrhea, pyrexia, rash, thrombocytopenia, cough, and vomiting.
- Severe peripheral sensory neuropathy and neutropenia were responsible for the majority of dose reductions and interruptions during the Adcetris (brentuximab vedotin) clinical trials. Fatal and serious cases of fever and neutropenia have been reported with Adcetris (brentuximab vedotin) when given with AVD. Primary prophylaxis with filgrastim is recommended by the manufacturer.
- Infusion reactions, Stevens-Johnson syndrome, and progressive multifocal leukoencephalopathy (PML) have also been reported with Adcetris (brentuximab vedotin).
- A boxed warning was added to the prescribing information for Adcetris (brentuximab vedotin) in January 2012 stating that JC virus infection resulting in PML and death can occur in patients treated with Adcetris (brentuximab vedotin).
- Coadministration of Adcetris (brentuximab vedotin) with strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole) may result in increased exposure to Adcetris (brentuximab vedotin), so close monitoring for adverse reactions is necessary.

Dosing Considerations [12]

- Adcetris (brentuximab vedotin) is given via intravenous infusion over 30 minutes.
- Dose delays and reductions are indicated for peripheral neuropathy and neutropenia.
- Adcetris (brentuximab vedotin) is contraindicated for concomitant use with bleomycin.
- FDA-labeled dosing by indication:

Indication	Recommended dose	Frequency and Duration
Previously untreated Stage III or IV cHL (adult)	1.2 mg/kg up to a max of 120 mg in combination with chemotherapy	Q2 weeks until a maximum of 12 doses (stop earlier if disease progression)
Previously untreated high-risk cHL (pediatric)	1.8 mg/kg up to a max of 180 mg in combination with chemotherapy	Q3 weeks until a maximum of 5 doses (stop earlier if disease progression)
cHL consolidation	1.8 mg/kg up to a max of 180 mg	Q3 weeks until a maximum of 16 doses (stop earlier if disease progression)
Relapsed cHL	1.8 mg/kg up to a max of 180 mg	Q3 weeks until disease progression
Previously untreated sALCL or other CD30-expressing PTCLs	1.8 mg/kg up to a max of 180 mg in combination with chemotherapy	Q3 weeks with each cycle of chemotherapy for 6 to 8 doses
Relapsed sALCL	1.8 mg/kg up to a max of 180 mg	Q3 weeks until disease progression
Relapsed pcALCL or CD30-expressing MF	1.8 mg/kg up to a max of 180 mg	Q3 weeks until a maximum of 16 doses (stop earlier if disease progression)

cHL = classical Hodgkin lymphoma; sALCL = systematic anaplastic large cell lymphoma; MF = mycoses fungoides; pcALCL = primary cutaneous anaplastic large cell lymphoma; PTCL = peripheral T-cell lymphoma

Appendix 1: International Prognostic Score (IPS) for Determining Risk Level in cHL [2]
Patients with High-Risk cHL have at least FOUR of the following risk factors:
• Male sex • Age ≥ 45 years • Stage IV disease • Hemoglobin < 10.5 g/dL • Lymphocyte count < 0.6 x 10^9/L, or < 8% of WBC • Leukocytosis (WBC ≥ 15,000/mm^3) • Serum albumin < 4 g/dL

Cross References
Medications for T-cell lymphoma, Medication Policy Manual, Policy No. dru705
PD-1 and PD-L1 Inhibitor Monoclonal Antibody Therapies, Medication Policy Manual, Policy No. 797

Codes	Number	Description
HCPCS	J9042	Injection, brentuximab vedotin (Adcetris), 1 mg

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Revision History

Revision Date	Revision Summary
3/6/2025	No changes to coverage criteria with this annual review.
12/12/2024	No criteria changes with this annual review.
12/7/2023	No criteria changes with this annual review.
6/15/2023	Effective 7/15/2023: • Modified first-line cHL criteria to allow coverage in high-risk disease in combination with cytotoxic chemotherapy, based on new indication in pediatric patients. • Updated quantity and duration limits.
12/9/2022	Effective 1/15/2023: • Updated cHL criteria to allow coverage in the first-line setting when used with in combination with AVD chemotherapy for stage 3 and 4 disease. • Updated standard policy template language.
6/17/2022	Clarified intent of coverage for cHL in the first-line setting. No updates to criteria.
1/20/2021	Updated continuation of therapy (COT) language. No changes to coverage criteria.
1/22/2020	• Added continuation of therapy (COT) criteria (no change to intent of coverage criteria). • The quantity limitations were rearranged by disease state rather than by dosing so they would parallel the order of the coverage criteria. Additionally, the authorization period section was also rearranged to better coincide with the quantity limitations. These changes were made to improve the efficiency of application of this policy. The overall intent of coverage was preserved.
1/31/2019	• The condition for at least one prior therapy for primary cutaneous ALCL (pcALCL) was removed (coverage is now allowed in the front-line setting). • Coverage was added for specific subtypes of CD30-expressing PTCLs based on a new FDA indication: sALCL, PTCL NOS, and AITL. • Quantity limits and authorization periods were added for the new indications for which coverage will be provided.
6/15/2018	• Added coverage criteria for front-line use in patients with high-risk, stage III or VI cHL when bleomycin is contraindicated. • Added coverage for primary cutaneous ALCL or CD30-expressing mycoses fungoides (new indications, rare diseases) and removed these conditions from the list of investigational uses. • Updated quantity and duration limits.
7/14/2017	Updated list of 'investigational' conditions (added AITL).
9/9/2016	No changes to coverage criteria with this annual update.
11/11/2011	New policy.

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Medication Policy Manual | **Policy No:** dru278

Topic: Marqibo, vincristine sulfate liposome injection | **Date of Origin:** September 24, 2012

Committee Approval Date: January 20, 2021 | **Next Review Date:** January 2022

Effective Date: April 1, 2021

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Liposomal vincristine (Marqibo) is a liposomal form of generic vincristine sulfate. It is an intravenous chemotherapy used to treat a specific type of leukemia.

PLEASE NOTE: This policy and the coverage criteria below do not apply to generic vincristine sulfate. Generic vincristine sulfate does not require pre-authorization.

Policy/Criteria

Most contracts require pre-authorization approval of liposomal vincristine (Marqibo) prior to coverage.

I. Continuation of therapy (COT): Liposomal vincristine (Marqibo) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 below must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 below must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Liposomal vincristine (Marqibo) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A and B below are met.

A. A diagnosis of **Philadelphia chromosome negative (Ph-negative) acute lymphoblastic leukemia (ALL)**.

AND

B. Disease has progressed after at least two prior regimens including at least one induction/maintenance and one relapsed/refractory regimen. (see *Appendix 1*)

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services does not consider liposomal vincristine (Marqibo) to be a self-administered medication.

B. Authorization may be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

IV. Liposomal vincristine (Marqibo) is considered investigational when used for all other conditions, including but not limited to:

A. Treatment-naïve acute lymphoblastic leukemia

B. Non-Hodgkin lymphomas (NHLs)**,** including diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma (MCL)

C. Hodgkin lymphoma

D. Metastatic melanoma

E. Pediatric cancers

F. Retinoblastoma

G. Ependymoma

H. Wilms' Tumor

I. Sarcoma, including rhabdomyosarcoma

Position Statement

- Liposomal vincristine (Marqibo) is generic vincristine sulfate, a vinca alkaloid chemotherapy agent, encapsulated in a fatty vehicle.
- Because liposomal vincristine (Marqibo) is a unique formulation of generic vincristine sulfate, there may be interest in using liposomal vincristine (Marqibo) in indications where generic vincristine sulfate has been shown to be effective. To date, there is a lack of evidence to determine the relative clinical benefit of liposomal vincristine (Marqibo) compared to generic vincristine sulfate.
- Like generic vincristine sulfate, liposomal vincristine (Marqibo) is contraindicated for intrathecal administration and in patients with demyelinating conditions. They are also both associated with serious adverse effects including neuropathy, myelosuppression, severe constipation and/or paralytic ileus, and tissue injury due to extravasation.

Regence Pharmacy Services performs independent analyses of oncology medication evidence. NCCN clinical practice guidelines assignment of a category 2a/b recommendation does not necessarily establish medically necessity. The Regence Pharmacy Services analysis and coverage policy may differ from NCCN clinical practice guidelines.

Clinical Efficacy

Acute Lymphoblastic Leukemia

- Liposomal vincristine (Marqibo) has not been shown to provide additional clinical benefit compared to currently existing therapies used in the treatment of ALL.
- Liposomal vincristine (Marqibo) was approved based on one unpublished phase II, single-arm study in 65 patients with Ph-negative ALL that had progressed following two or more anti-leukemia therapies. [1]
    * The primary endpoint evaluated in this study was complete response plus complete response without full platelet recovery.
    * Ten (15.4%) subjects achieved the combined primary endpoint. Three (4.6%) subjects achieved complete response, while seven (10.8%) achieved complete response without full platelet recovery.
- One additional published phase II study evaluated overall response rate in 16 patients with refractory ALL. [2]
    * Treatment with liposomal vincristine (Marqibo) was the first salvage attempt in 11 patients, the second salvage attempt in 3 patients, and the third salvage attempt in 2 patients.
    * The overall response rate in the fourteen evaluable patients was 14% (1 complete responder; 1 partial responder).
- Liposomal vincristine (Marqibo) was studied in twenty adult patients with newly-diagnosed, B-cell ALL given as part of a hyper-CMAD regimen. This regimen was found to have good activity based on complete molecular response rates; however, the study only had a single arm (non-comparative) so it is not known if it offers any improvement in efficacy or safety over generic vincristine sulfate. [3]
- The National Comprehensive Cancer Network (NCCN) ALL guideline lists liposomal vincristine (Marqibo) among several category 2A recommendations for relapsed or refractory Ph-negative ALL. [4]

Non-Hodgkin Lymphoma (NHL)

- Liposomal vincristine (Marqibo) has not been shown to provide additional clinical benefit compared to currently existing therapies used in the treatment of NHLs.
- Two preliminary, early-phase studies were identified that evaluate liposomal vincristine (Marqibo) in refractory NHL, including large B-cell lymphoma and mantle cell lymphoma. The studies are small, uncontrolled, and evaluated tumor response. No clinical benefit has been demonstrated to date in these populations. [5,6]
- The NCCN does <u>not</u> list liposomal vincristine (Marqibo) among the treatment options for relapsed/refractory NHLs. [7]

Other Uses

- Liposomal vincristine (Marqibo) is currently being studied in a variety of other cancers including Hodgkin lymphoma, metastatic melanoma, non-Hodgkin's lymphomas (including diffuse large B-cell lymphoma and mantle cell lymphoma), acute myeloid leukemia (AML), and several pediatric cancers. [8]

- Liposomal vincristine (Marqibo) is considered investigational in the abovementioned cancers due to the low level of available evidence in these settings.

Safety [1]

- The safety profile for liposomal vincristine (Marqibo) appears similar to generic vincristine sulfate.
- Boxed warnings for liposomal vincristine (Marqibo) include potential death with intrathecal use and potential overdose if confused with generic vincristine as the dosing recommendations are different.
- Additional warnings include neuropathy, myelosuppression, tumor lysis syndrome, severe constipation and/or paralytic ileus, severe fatigue, hepatotoxicity, embryofetal toxicity, and tissue injury due to extravasation.
- Liposomal vincristine (Marqibo) is contraindicated in patients with demyelinating conditions including Charcot-Marie-Tooth syndrome.
- The most commonly reported adverse reactions (incidence ≥ 30%) in clinical studies include constipation, nausea, pyrexia, fatigue, peripheral neuropathy, febrile neutropenia, diarrhea, anemia, decreased appetite, and insomnia.

Dosing and Administration [1]

- Liposomal vincristine (Marqibo) is administered at a dose of 2.25 mg/m^2 intravenously over 1 hour once every 7 days.
- Liposomal vincristine (Marqibo) may be fatal if administered intrathecally.
- Dosing recommendations for liposomal vincristine (Marqibo) are different from those for generic vincristine; therefore, the drug name and dose should be verified prior to preparation and administration.
- Liposomal vincristine (Marqibo) requires approximately 60 to 90 minutes of preparation time and must be done according to aseptic technique in a biological safety cabinet.
- Dosing modification is recommended for patients who experience liposomal vincristine (Marqibo)-related peripheral neuropathy.

Cross References
Blincyto, blinatumomab, Medication Policy Manual, Policy No. dru388

Codes	**Number**	**Description**
HCPCS	J9370	Injection, vincristine sulfate (non-liposomal generic)
HCPCS	J9371	Injection, vincristine sulfate liposome (Marqibo), 1 mg

Appendix 1: Therapies/Treatment Regimens for Philadelphia Chromosome Negative Acute Lymphoblastic Leukemia [Ph (-) ALL] [4]
Commonly used chemotherapy induction regimens [a, b]
anthracycline (daunorubicin/doxorubicin) + generic vincristine sulfate + steroid (prednisone/dexamethasone) + asparaginase or rituximab ± other (e.g. cyclophosphamide, cytarabine, 6-mercaptopurine)
Maintenance regimens
methotrexate + 6-mercaptopurine + generic vincristine sulfate/prednisone pulses
Relapsed / refractory regimens
blinatumomab (Blincyto)
inotuzumab ozogamicin (Besponsa) [for B-ALL]
tisagenlecleucel (Kymriah) [for B-ALL]
clofarabine (Clolar)
cytarabine-containing regimens
alkylator combination regimens (e.g. etoposide + ifosfamide + mitoxantrone)
nelarabine (Arranon) [T ALL only]
cyclophosphamide + generic vincristine sulfate + doxorubicin + dexamethasone + asparaginase + cytarabine/methotrexate (augmented hyper-CVAD)
liposomal vincristine (Marqibo)

[a] Systemic regimens, not including intrathecal (IT) CNS prophylaxis.
[b] Variable, based on age and underlying patient characteristics.

References

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Revision History

Revision Date	Revision Summary
1/20/2021	Updated continuation of therapy (COT) language. No changes to coverage criteria.
06/15/2020	Removed references to brand Rituxan from policy, to account for upcoming changes in biosimilars policy (dru620).
1/22/2020	Added continuation of therapy (COT) criteria (no change to intent of coverage criteria).
1/31/2018	No criteria changes with this annual update.
9/21/2018	No changes with this annual update.
9/8/2017	The list of conditions considered investigational uses was updated.
8/12/2016	No changes with this annual update.
09/24/2012	New policy

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Medication Policy Manual

Policy No: dru279

Topic: Zaltrap, ziv-aflibercept

Date of Origin: September 24, 2012

Committee Approval Date: June 20, 2024

Next Review Date: 2025

Effective Date: September 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Zaltrap (ziv-aflibercept) is an intravenous (IV) medication, a Vascular Endothelial Growth Factor (VEGF) inhibitor, used in the treatment of colon cancer.

Policy/Criteria

Most contracts require pre-authorization approval of Zaltrap (ziv-aflibercept) prior to coverage.

I. Continuation of therapy (COT): Zaltrap (ziv-aflibercept) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Zaltrap (ziv-aflibercept) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) confirming that criteria A, B, and C below are met:

A. A diagnosis of **metastatic colorectal cancer**.

AND

B. Prior treatment with an Eloxatin (oxaliplatin)-containing regimen has been ineffective or not tolerated.

AND

C. Prior treatment with bevacizumab has been ineffective, contraindicated, or not tolerated.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Zaltrap (ziv-aflibercept) coverable only under the medical benefit (as a provider-administered medication).

B. Authorization **may** be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, including disease stability or improvement relative to baseline symptoms.

IV. Zaltrap (ziv-aflibercept) is considered investigational when used for all other conditions, including but not limited to:

A. Gastroesophageal cancers.

B. Kidney cancer.

C. Leukemia.

D. Lung cancer [small cell (SCLC), and non-small cell lung cancers (NSCLC)].

E. Lymphoma.

F. Ovarian cancer.

G. Pancreatic cancer.

H. Prostate cancer.

I. Thyroid cancer.

Position Statement

- Zaltrap (ziv-aflibercept) is an intravenously infused medication that inhibits Vascular Endothelial Growth Factor (VEGF) thereby preventing the formation of new blood vessels and halting cell growth.
- The intent of this policy is to cover Zaltrap (ziv-aflibercept) for the indications, regimen, and dose for which it has been shown to be safe and effective, as detailed in the coverage criteria.
- Zaltrap (ziv-aflibercept) demonstrated an improvement in overall survival in metastatic colorectal cancer that was previously treated with an oxaliplatin-containing regimen.
- Zaltrap (ziv-aflibercept) was studied in combination with 5-fluorouracil, leucovorin and irinotecan (FOLFIRI).
- Bevacizumab (Avastin, biosimilars) is another VEGF inhibitor approved for the treatment of metastatic colorectal cancer in combination with 5-fluorouracil based chemotherapy.
- There is insufficient evidence to establish the comparative efficacy and safety of bevacizumab (Avastin, biosimilars) and Zaltrap (ziv-aflibercept).
- For our health plan members, bevacizumab (Avastin, biosimilars) is the preferred medication among the VEGF inhibitors used to treat metastatic colorectal cancer.

- The safety and effectiveness of Zaltrap (ziv-aflibercept) have not been established in conditions other than metastatic colorectal cancer.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy

Zaltrap (ziv-aflibercept) demonstrated improved overall survival in patients with metastatic colorectal cancer (CRC) previously treated with an oxaliplatin-containing regimen.

- A single, randomized controlled trial compared Zaltrap (ziv-aflibercept) in combination with 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI) to FOLFIRI alone in the treatment of patients with metastatic colorectal cancer that was resistant to, or had progressed following, and oxaliplatin-containing regimen. [1,2]
    * The primary endpoint of the study was overall survival (OS). The addition of Zaltrap (ziv-aflibercept) to FOLFIRI improved OS by 1.44 months compared to FOLFIRI alone (12.06 versus 13.5 months, respectively; p = 0.0032).
    * Approximately 30% of randomized patients had received prior treatment with bevacizumab.
- The National Comprehensive Cancer Network (NCCN) Colon and Rectal Cancer treatment guidelines list Zaltrap (ziv-aflibercept) as an option after the first progression of metastatic colon or rectal cancer. NCCN recommends that Zaltrap (ziv-aflibercept) be used in combination with FOLFIRI or irinotecan. Bevacizumab is recommended as a preferred recommendation in this treatment setting. Additionally, bevacizumab has a recommendation for initial treatment of advanced or metastatic colorectal cancer in combination with FOLFOX or CapeOX. [3]

Use in Other Conditions [4]

Zaltrap (ziv-aflibercept) is currently being studied for treatment of a variety of cancers including: leukemia, lung cancer (small cell and non-small cell), lymphoma, ovarian cancer, pancreatic cancer, prostate cancer and thyroid cancer. There are currently no published studies supporting the safety or efficacy of Zaltrap (ziv-aflibercept) in these cancers. Preliminary results reported on clinicaltrials.gov show a lack of benefit with Zaltrap (ziv-aflibercept) in non-small cell lung cancer, ovarian cancer, and prostate cancer.

Safety [1]

- Zaltrap (ziv-aflibercept) has Boxed Warnings for risk of hemorrhage, gastrointestinal perforation, and compromised wound healing.
- Other serious adverse effects reported with Zaltrap (ziv-aflibercept) include fistula formation, hypertension, arterial thromboembolic events, proteinuria, neutropenia, diarrhea and dehydration, and reversible posterior leukoencephalopathy syndrome.

Dosing [1]

- The usual dose of Zaltrap (ziv-aflibercept) is 4 mg/kg given by intravenous infusion over 1 hour every 2 weeks.
- Zaltrap (ziv-aflibercept) is indicated for use in combination with 5-fluorouracil, leucovorin and irinotecan (FOLFIRI).

Cross References
Products with Therapeutically Equivalent Biosimilars/Reference Products, Medication Policy Manual, Policy No. dru620
BRAF inhibitors, Medication Policy Manual No. 728
Cyramza, ramucirumab, Medication Policy Manual No. dru355
Keytruda, pembrolizumab, Medication Policy Manual No. dru367
Opdivo, nivolumab, Medication Policy Manual No. dru390
Tukysa, tucatinib, Medication Policy Manual, Policy No. dru646
Yervoy ipilimumab, Medication Policy Manual No. dru238

Codes	**Number**	**Description**
HCPCS	J9400	Injection, ziv-aflibercept (Zaltrap), 1 mg

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Revision History

Revision Date	Revision Summary
6/20/2024	No criteria changes with this annual review.
6/15/2023	There were no changes to the coverage criteria with this annual update.
6/17/2022	There were no changes to the coverage criteria with this annual update. *Note: Revisions were made to update to current standard policy language; however, there was no change to the intent of this policy.*
7/16/2021	• No changes to coverage criteria with this annual review. • The COT language was updated to the standard template language (no change to intent).
7/22/2020	Added continuation of therapy (COT) language (no change to policy intent). Removed references to brand Avastin to account for upcoming changes to biosimilars policy (dru620).
7/24/2019	Updated policy with standard language (no change to policy intent).
11/16/2018	No criteria changes with this annual update.
11/10/2017	No criteria changes with this annual update.
8/12/2016	No criteria changes with this annual update.

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Medication Policy Manual **Policy No:** dru281

Topic: pertuzumab-containing medications:

- Perjeta, pertuzumab
- Phesgo, pertuzumab/trastuzumab/hyaluronidase

Date of Origin: September 24, 2012

Committee Approval Date: June 20, 2024 **Next Review Date:** 2025

Effective Date: July 15, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Perjeta (pertuzumab) is a monoclonal antibody used in the treatment of HER2-positive breast cancer. It is given via intravenous infusion in combination with trastuzumab plus chemotherapy. Phesgo (pertuzumab/trastuzumab/hyaluronidase) is a combination of monoclonal antibodies used in the treatment of HER2-positive breast cancer that can be given subcutaneously under the skin.

Policy/Criteria

Most contracts require pre-authorization approval of pertuzumab-containing medications prior to coverage.

I. Continuation of therapy (COT): Pertuzumab-containing medications may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Pertuzumab-containing medications may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) confirming that one of the following criterion A, B, or C below is met:

A. **Metastatic Breast Cancer:** A diagnosis of HER2-positive metastatic breast cancer when criteria 1 and 2 below are met:

1. Pertuzumab-containing medications are used in one of the two treatment settings described below:

a. Patient has had no prior therapy for HER2-positive metastatic breast cancer.

OR

b. Patient has received one prior therapy for metastatic breast cancer that included trastuzumab plus chemotherapy in the absence of Perjeta (pertuzumab).

AND

2. **Perjeta Only:** Perjeta (pertuzumab) is used concomitantly with trastuzumab and chemotherapy (e.g., docetaxel).

OR

B. **Neoadjuvant (pre-operative) Use in Breast Cancer:** A diagnosis of HER2-positive locally advanced, inflammatory, or early-stage breast cancer when criteria 1, 2, and 3 below are met:

1. Pertuzumab-containing medications are used preoperatively prior to resection of the breast tumor (neoadjuvant setting).

AND

2. Pertuzumab-containing medications are used concomitantly with chemotherapy (e.g., docetaxel).

AND

3. **Perjeta Only:** Perjeta (pertuzumab) is also used concomitantly with trastuzumab.

OR

C. **Adjuvant (post-operative) Use in Breast Cancer:** A diagnosis of HER2-positive locally advanced, inflammatory, or early-stage breast cancer when criteria 1 through 6 below are met:

1. Pertuzumab-containing medications are used post-operatively after resection of the breast tumor (adjuvant setting).

AND

2. One of the two following settings (a or b):

a. The patient is node-positive (based on surgical pathology report or attestation) and all of the following (i through iv):

i. The patient did **not** receive neoadjuvant chemotherapy.

AND

ii. The patient has had no prior HER2-directed chemotherapy [such as trastuzumab, Perjeta (pertuzumab), or Kadcyla (ado-trastuzumab emtansine)].

AND

iii. Pertuzumab-containing medications are used concomitantly with chemotherapy (e.g., docetaxel).

AND

iv. **Perjeta Only:** Perjeta (pertuzumab) is also used concomitantly with trastuzumab.

OR

b. The patient was on adjuvant Kadcyla (ado-trastuzumab emtansine) for residual disease and both of the following (i and ii)

i. Adjuvant Kadcyla (ado-trastuzumab emtansine) was not tolerated.

AND

ii. **Perjeta Only:** Perjeta (pertuzumab) is used concomitantly with trastuzumab.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers pertuzumab-containing medications coverable only under the medical benefit (as a provider-administered medication).

B. When preauthorization is approved, pertuzumab-containing medications will be approved as follows:

1. Metastatic setting:

a. Perjeta (pertuzumab): Initial dose of 840 mg, followed by subsequent doses of 420 mg every 3 weeks until disease progression. Perjeta (pertuzumab) should be discontinued if trastuzumab is discontinued.

b. Phesgo (pertuzumab/trastuzumab/hyaluronidase): Initial dose of 1,200 mg pertuzumab, 600 mg trastuzumab, and 30,000 units hyaluronidase followed every 3 weeks by subsequent doses of 600 mg pertuzumab, 600 mg trastuzumab, and 20,000 units hyaluronidase until disease progression.

2. Neoadjuvant setting:

a. Perjeta (pertuzumab): Initial dose of 840 mg, followed by 420 mg every 3 weeks for up to six doses prior to surgery. Perjeta (pertuzumab) should be discontinued if trastuzumab is discontinued.

b. Phesgo (pertuzumab/trastuzumab/hyaluronidase): Initial dose of 1,200 mg pertuzumab, 600 mg trastuzumab, and 30,000 units hyaluronidase followed every 3 weeks by subsequent doses of 600 mg pertuzumab, 600 mg trastuzumab, and 20,000 units hyaluronidase preoperatively for 3 to 6 cycles.

3. Adjuvant setting:

a. Perjeta (pertuzumab): Initial dose of 840 mg, followed by 420 mg every 3 weeks for up to 18 doses (one year of combined neoadjuvant and adjuvant therapy total) or until disease progression.

b. Phesgo (pertuzumab/trastuzumab/hyaluronidase): Initial dose of 1,200 mg pertuzumab, 600 mg trastuzumab, and 30,000 units

hyaluronidase followed every 3 weeks by subsequent doses of 600 mg pertuzumab, 600 mg trastuzumab, and 20,000 units hyaluronidase postoperatively for a total of 1 year (up to 18 cycles) or until disease progression.

C. Authorization **may** be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

IV. Pertuzumab-containing medications are considered not medically necessary when used for node-negative HER2-positive breast cancer treatment in the adjuvant (after surgical resection) setting.

V. Pertuzumab-containing medications are considered investigational when:

A. Perjeta (pertuzumab) is not administered in conjunction with trastuzumab.

B. Used beyond the second-line treatment setting for metastatic breast cancer.

C. Used in the adjuvant setting, after the patient has received neoadjuvant therapy.

D. Gastric cancer.

E. HER2-negative breast cancer.

F. Ovarian cancer.

G. Colorectal cancer.

H. Non-small cell lung cancer.

Position Statement

- Perjeta (pertuzumab), a monoclonal antibody that prevents growth of cancer cells via its blockade of HER2 receptors, is approved for the treatment of HER2-positive metastatic breast cancer (mBC); as a neoadjuvant therapy (used prior to surgical resection of a tumor) for locally advanced, inflammatory, or early-stage HER2-positive breast cancer; and as an adjuvant therapy (used after surgical resection of a tumor) for non-metastatic, invasive, HER2-positive breast cancer at high risk of recurrence.
- Perjeta (pertuzumab) binds to a different area on HER2 receptors than trastuzumab. In some breast cancer settings, the two medications used in combination may provide greater antitumor activity than trastuzumab alone.
- Phesgo (pertuzumab/trastuzumab/hyaluronidase) is a fixed dose combination of pertuzumab and trastuzumab with hyaluronidase, an endoglycosidase, combined in a formulation that can be given subcutaneously.
- The intent of this policy is to cover pertuzumab-containing medications (Perjeta, Phesgo) for the indications, regimen, and dose for which it has been shown to be safe and effective, as detailed in the coverage criteria, with consideration for other available treatment options.

    * Effective is defined by having a known health benefit and/or an additional health benefit relative to available treatment alternatives.
    * Where there is lack of proven additional benefit for Perjeta (pertuzumab) relative to alternatives, and/or a lack of a demonstrated health outcome (such as overall survival), use of Perjeta (pertuzumab) is not coverable ("not medically necessary" or "investigational").
- It is important to note that the fact that a medication is FDA approved for a specific indication does not, in itself, make the treatment medically reasonable and necessary.

Metastatic breast cancer (mBC)

- The combination of Perjeta (pertuzumab), trastuzumab and docetaxel has been shown to significantly improve median overall survival (OS) as a first-line therapy for HER2-positive mBC relative to trastuzumab and docetaxel alone.
- The evidence for Perjeta (pertuzumab) in the second-line HER2-positive mBC setting is of poor quality. However, as it is rapidly becoming the standard of care, coverage is provided in the second-line setting when Perjeta (pertuzumab) was not used with trastuzumab plus chemotherapy in the first-line mBC setting.

Non-metastatic breast cancer (locally advanced, inflammatory, or early-stage)

- *Neoadjuvant*: Evidence for Perjeta (pertuzumab) in the neoadjuvant setting (when given for 3 to 6 doses prior to surgical resection of the breast tumor) is based on a surrogate endpoint (the absence of invasive cancer in the breast and lymph nodes).[1] It is not known if it improves survival, or any other clinically relevant endpoint, when used in this setting. There is no evidence to support the use of more than 6 doses of neoadjuvant Perjeta (pertuzumab).
- *Adjuvant*: The use of Perjeta (pertuzumab) as an add-on to adjuvant chemotherapy plus trastuzumab was FDA-approved based on the results of the APHINITY trial in patients who received no prior neoadjuvant therapy, such as neoadjuvant chemotherapy. [2]
    * In patients who did not receive neoadjuvant therapy, the addition of Perjeta (pertuzumab) to a standard adjuvant regimen results in a nominal improvement in invasive disease-free survival (iDFS) relative to standard therapy (iDFS of 91% vs 88% at 6 years). Though statistically different, this difference is not likely clinically relevant iDFS is a surrogate endpoint which has not been shown to reliably predict clinically relevant outcomes such as a decrease in metastatic disease recurrence or improved OS.
    * To date there is no evidence demonstrating an improvement in OS when Perjeta (pertuzumab) is added to the standard adjuvant regimen (6-year overall survival were 95% vs. 94%).
    * The reporting of preliminary results at 3 years in an early-stage BC population is earlier than the typical 5-year standard. Use of preliminary evidence leads to uncertainty when estimating the net health benefit of this regimen. This can lead to over-estimation of benefit and underestimation of harms.
    * Because the results from this trial are underwhelming, there has been significant focus on subgroup analyses, particularly related to the node-positive subpopulation.

- After an interim analysis suggested a possibility of futility, recruitment of subjects in APHINITY was changed to exclude node-negative women during the trial. Therefore, the application of any benefit in node-negative patients is questionable.
- The hazard ratio in this population suggests a greater likelihood of improvement in iDFS with the addition of Perjeta (pertuzumab) to a standard adjuvant regimen; however, the improvement in iDFS is small and has only been shown in node-positive women on an *a priori* basis.
- Other subgroup analyses that suggested no benefit was associated with treatment in other important populations, such as in pre-menopausal women.
- As node-negative women were excluded from recruitment during the trial and there is no evidence of benefit, the addition of Perjeta (pertuzumab) to standard TCH therapy in this population is considered unproven.

- *Adjuvant, after neoadjuvant therapy*:
  * Women who received neoadjuvant treatment with Perjeta (pertuzumab) or other neoadjuvant chemotherapy prior to surgery were excluded from the APHINITY trial;[2] therefore, it is not known if Perjeta (pertuzumab) in the adjuvant setting is beneficial in this population (after neoadjuvant chemotherapy).
  * Current standard of care for women treated with neoadjuvant chemotherapy with residual disease at the time of surgery is adjuvant Kadcyla (ado-trastuzumab emtansine). The use of pertuzumab in this setting is unproven.
  * The optimal approach to treatment of women who achieve a pathologic complete response (pCR) after neoadjuvant chemotherapy has not been prospectively studied. The NeoSphere trial[1] reported 5-year PFS of 86% in women who received docetaxel, trastuzumab, and pertuzumab in the neoadjuvant setting followed by no adjuvant therapy. It is unknown how this compares to the current standard of care (neoadjuvant TCHP followed by adjuvant trastuzumab to complete 1 year of HER-2 directed therapy), particularly for women who achieve a pCR after neo-adjuvant therapy.
  * Because the addition of Perjeta (pertuzumab) to adjuvant therapy has only been shown to improve outcomes in a narrow group of subjects, extrapolation of these study results outside of the setting in which it has shown benefit is considered investigational and not covered under most benefits.
- NCCN lists the following recommendations:
  * The addition of Perjeta (pertuzumab) to a standard adjuvant regimen is a category 2A recommendation (independent of node-negative vs. node-positive). The use of trastuzumab alone is listed as a category 1 (highest level) recommendation. [3]
  * For patients who received neoadjuvant chemotherapy and are found to have residual disease, adjuvant Kadcyla (ado-trastuzumab emtansine) is a category 1 recommendation. In the infrequent scenario in which Kadcyla (ado-trastuzumab emtansine) is not tolerated, switching to adjuvant trastuzumab with Perjeta (pertuzumab) is a category 1 recommendation.

- Although NCCN does not differentiate adjuvant therapy recommendations for node-negative versus node-positive patients, ASCO guidelines state the APHINITY trial showed no clinically meaningful benefit in node-negative patients.
- Perjeta (pertuzumab) has not been shown to be effective when used alone (i.e., not in combination with trastuzumab) or in the treatment of other types of cancer.
- Perjeta (pertuzumab) has been shown to be safe and effective when dosed as follows: an initial dose of 840 mg via intravenous infusion, followed by 420 mg every three weeks.
- The safety of administering more than six doses (cycles) of Perjeta (pertuzumab) in early breast cancer (neoadjuvant setting) has not been established.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy

HER2-POSITIVE METASTATIC BREAST CANCER

- There is fair confidence in the evidence that the addition of Perjeta (pertuzumab) to a standard trastuzumab-containing regimen improves median overall survival (OS) in HER2-positive metastatic breast cancer (BC). [4]
    * A single, phase 3 pivotal trial compared Perjeta (pertuzumab) plus trastuzumab plus docetaxel with trastuzumab plus docetaxel alone in the HER2-positive metastatic BC setting.
        - The trial enrolled patients who had no prior chemotherapy or trastuzumab in the metastatic setting. Prior trastuzumab was allowed in the adjuvant or neoadjuvant setting if 12 months had passed between completion of adjuvant/neoadjuvant therapy and diagnosis of metastatic BC.

- In the initial efficacy analysis, median PFS was prolonged by approximately 6 months in the Perjeta (pertuzumab) treatment arm. [5]
- In a final survival analysis of this trial, a significant improvement in median OS was demonstrated. Subjects in the Perjeta (pertuzumab) arm had a median OS of 56.5 months versus 40.8 months in the control group [hazard ratio of 0.68; 95% CI (0.56, 0.84); p < 0.001]. [6]

* The evidence for Perjeta (pertuzumab) in patients who have had progression while receiving prior HER2-blocking therapy is of poor quality. [7]
  - An uncontrolled study trial evaluated the combination of Perjeta (pertuzumab) and trastuzumab in patients who had progression of their HER2-positive metastatic BC on prior trastuzumab-based therapy.
  - The evidence from this trial is of poor quality because there was no comparator arm or blinding employed in the study. The effects of bias, confounding, and chance cannot be ruled out.
  - The study evaluated overall response rates (ORR) in 58 patients.
  - The authors reported a 24% ORR and a median PFS of 5.5 months.

NON-METASTATIC (EARLY BREAST CANCER), PRIOR TO SURGICAL RESECTION (NEOADJUVANT SETTING)

- The evidence of efficacy for Perjeta (pertuzumab) in the neoadjuvant setting for locally advanced, inflammatory, or early-stage BC is of low quality. [1 8]
  * An open-label trial evaluated pathological complete response (pCR) rates for the combination of Perjeta (pertuzumab)/trastuzumab docetaxel versus trastuzumab/docetaxel alone as neoadjuvant therapy for women with early-stage HER2-positive BC.
  * Therapy was given preoperatively for 3 to 6 cycles prior to tumor resection [Perjeta (pertuzumab) was administered every 3 weeks for 3 to 6 doses].
  * Pathological complete response is defined as the absence of invasive cancer in the breast and lymph nodes. It is unknown if pCR is an accurate predictor of OS in BC.
  * The effect of neoadjuvant Perjeta (pertuzumab) on OS has not been evaluated.
  * There is no evidence to support the use of more than 6 cycles of neoadjuvant Perjeta (pertuzumab). Therefore, the use of more than 6 cycles is not coverable.

ADJUVANT (POST SURGICAL RESECTION) – NON-METASTATIC HER2-POSITIVE BREAST CANCER SETTING

- A multicenter, randomized, double-blind, placebo-controlled APHINITY trial (N=4,805) compared Perjeta (pertuzumab) with placebo each added to standard adjuvant chemotherapy plus 1 year of treatment with trastuzumab in patients with HER2-positive early breast cancer. [2]
  * The 3-year rate of invasive-disease-free survival (iDFS) was 94.1% in the Perjeta (pertuzumab) group and 93.2% in the placebo group [hazard ratio 0.81; 95% CI (0.66, 1.0); p=0.045). Although statistically different, this very small difference is not likely clinically relevant.

    * iDFS is a surrogate endpoint that has not been shown to correlate with a clinically meaningful outcome such as decreased metastatic recurrence or improved overall survival.
    * No overall survival difference has been demonstrated between groups to date.
    * A 3-year follow-up in this population is considered preliminary. A 5-year follow up is a more typical timeframe. Use of preliminary results leads to uncertainty in the net clinical benefit (potential for harms relative to potential for benefit) assessment.
    * Subset analyses in patients with either node-positive disease, or hormone receptor-negative disease appears to show a small benefit in iDFS in the Perjeta (pertuzumab) versus placebo groups; however, the potential for benefit is very small and is likely an overestimate due to enrichment of the study population with node-positive patients. A protocol amendment to stop enrolling node-negative patients was made late in the study because it was noted that this subpopulation was not experiencing any benefit with Perjeta (pertuzumab).
- Overall, the addition of Perjeta (pertuzumab) to a standard adjuvant treatment regimen has not been shown to improve any clinically relevant outcome, may increase the likelihood of side effects to adjuvant therapy, and is associated with a higher cost of care.

USE IN OTHER CONDITIONS

- Early phase 2 trials that studied pertuzumab (Perjeta, previously referred to as Omnitarg) showed that it had only limited activity as a single agent in ovarian, breast, and prostate cancers. [9] It is, therefore, unlikely to be effective when used alone.
- A recently published phase II trial found no benefit in adding Perjeta (pertuzumab) to standard chemotherapy in women with recurrent ovarian cancer. [10]
- A small (n = 30), early phase pharmacokinetic and safety study was conducted with Perjeta (pertuzumab) in patients with advanced gastric or gastro-esophageal junction cancer. A larger, phase 3 study is planned to evaluate the safety and efficacy of Perjeta (pertuzumab) in this condition. [11]
- A small phase 2a basket trial evaluated pertuzumab in HER2-amplified metastatic colorectal cancer. Although 32% of patients had a response (ORR) on pertuzumab plus trastuzumab therapy, there is insufficient evidence to establish the benefit of this combination therapy for colon cancer. While these preliminary results are promising, there is no evidence of benefit on clinically meaningful outcomes, such as increased overall survival. [12]
- The evidence for pertuzumab in HER2-positive non-small cell lung cancer is limited to one phase 2 trial. No benefit was observed with pertuzumab treatment on the primary endpoints of complete response and partial response. Additional trials are ongoing. [13]

GUIDELINES

- National Comprehensive Cancer Network (NCCN) BC guideline recommendations for pertuzumab in HER2-positive BC: [3]
    * ***Metastatic setting:*** The combination of Perjeta (pertuzumab) plus trastuzumab plus docetaxel is listed as a category 1 recommendation for the first-line

treatment of HER2-positive metastatic BC. The regimen gets a category 2A recommendation if paclitaxel is substituted for docetaxel. The guideline also states that Perjeta (pertuzumab) may be given in combination with trastuzumab in the second-line metastatic treatment setting if patients were previously treated in the first-line metastatic setting with trastuzumab plus chemotherapy in the absence of Perjeta (pertuzumab) [category 2A recommendation].

* ***Neoadjuvant setting:*** The use of Perjeta (pertuzumab) in the neoadjuvant setting is listed as a category 2A recommendation when used prior to surgery for early BC when administered concomitantly with a taxane plus trastuzumab.
* ***Adjuvant setting:***
  - The preferred, category 1 recommended adjuvant regimen for non-metastatic, invasive HER2-positive BC is adjunctive chemotherapy followed by paclitaxel plus trastuzumab. The addition of Perjeta (pertuzumab) to a standard adjuvant regimen is listed as a category 2A recommendation (independent of node-negative vs. node-positive).
  - For patients who received neoadjuvant chemotherapy and are found to have residual disease, adjuvant Kadcyla (ado-trastuzumab emtansine) is a category 1 recommendation. In the infrequent scenario in which Kadcyla (ado-trastuzumab emtansine) is not tolerated, switching to adjuvant trastuzumab with Perjeta (pertuzumab) is a category 1 recommendation.

- The American Society of Clinical Oncology (ASCO) breast cancer guideline states that one year of adjuvant Perjeta (pertuzumab) may be added to trastuzumab-based combination chemotherapy for patients with early-stage, HER2-positive breast cancer (moderate strength recommendation). Qualifying statements include: [14]
  * The recommendation is based on a modest disease-free benefit in patient with node-positive disease.
  * No benefit was observed in node-negative patients, and no survival benefit has been shown to date.
  * There is no data to guide the length of Perjeta (pertuzumab) therapy in patients with a complete pathologic response to neoadjuvant therapy.
- The National Institute for Health and Care Excellence (NICE) technical appraisal concluded that there is uncertainty regarding the potential for benefit with Perjeta (pertuzumab) when used in the adjuvant treatment of early-stage HER2-postive breast cancer. Reasons for the uncertainty include: [15]
  * Improvement in invasive disease-free survival is marginal and there is uncertainty in the estimate of effect.
  * There is uncertainty as to whether the invasive disease-free survival endpoint reliably predicts metastatic recurrence or overall survival benefit. A related surrogate endpoint, pathological complete response, was not associated with improved OS over the long term in a previous study in early breast cancer at high risk of recurrence.

* The overall survival data are immature, and there is currently no apparent difference between treatment groups for this endpoint.
* The evidence for increased evidence in the node-positive and hormone receptor-negative subgroups is not convincing because of the non-significant test for interaction in each of these subgroups (implies that there is no evidence that the hazard ratio comparing Perjeta (pertuzumab) versus placebo showed a difference in the subgroups).

Safety *[8 16]*

- Pertuzumab-containing medications (Perjeta, Phesgo) carry a Boxed Warning for embryo-fetal death and birth defects and is listed as a pregnancy Category D. They also carry a Boxed Warning describing the risk of clinical cardiac failure including left ventricular dysfunction and congestive heart failure.
- Common adverse effects when Perjeta (pertuzumab) is combined with trastuzumab plus docetaxel (≥ 30% incidence) include diarrhea, alopecia, neutropenia, nausea, fatigue, rash, and peripheral neuropathy.
- Pertuzumab-containing medications (Perjeta, Phesgo) should be withheld for a left ventricular ejection fraction (LVEF) of < 40% or for a LVEF of 40% to 45% with a 10% absolute decrease below pretreatment values.

Dosing *[8 16]*

- The initial dose of Perjeta (pertuzumab) is 840 mg administered as a 60-minute infusion. This is followed every 3 weeks thereafter with 420 mg doses administered over 30 to 60 minutes.
- The initial dose of Phesgo (pertuzumab/trastuzumab/hyaluronidase) is 1,200 mg pertuzumab, 600 mg trastuzumab, and 30,000 units hyaluronidase administered subcutaneously over approximately 8 minutes, followed every 3 weeks by a dose of 600 mg pertuzumab, 600 mg trastuzumab, and 20,000 units hyaluronidase administered subcutaneously over approximately 5 minutes.
- In the neoadjuvant HER2-positive BC setting, pertuzumab-containing medications (Perjeta, Phesgo) are given preoperatively every 3 weeks for 3 to 6 doses. The safety of pertuzumab-containing medications (Perjeta, Phesgo) given for more than 6 doses for early BC has not been established.
- When used in the adjuvant setting (after surgical resection), pertuzumab-containing medications (Perjeta, Phesgo) are given every three weeks for a total of one year (up to 18 cycles). It should not be continued if trastuzumab is stopped. [Note: Use in this setting is considered 'not medically necessary' based on health plan contracts]

Cross References
BlueCross BlueShield Association Medical Policy, 5.01.20 - Pertuzumab for Treatment of Malignancies [November 2022]
Products with Therapeutically Equivalent Biosimilars/Reference Products, Medication Policy Manual, Policy No. dru620
Enhertu, fam-trastuzumab deruxtecan-nxki, Medication Policy Manual, Policy No. dru623
Kadcyla, ado-trastuzumab emtansine, Medication Policy Manual, Policy No. dru298
Nerlynx, neratinib, Medication Policy Manual, Policy No. dru520
Tukysa, tucatinib, Medication Policy Manual, Policy No. dru646
lapatinib (generic, Tykerb), Medication Policy Manual, Policy No. dru145

Codes	Number	Description
HCPCS	J9306	Injection, pertuzumab (Perjeta), 1 mg
HCPCS	J9316	Injection, pertuzumab, trastuzumab, and hyaluronidase-zzxf (Phesgo), per 10 mg

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8. Perjeta (pertuzumab) [package insert]. Genentech, Inc.; South San Francisco, CA; February 2021.

9. Genentech, Inc. Press Release: Data From Omnitarg Clinical Program Presented at American Society of Clinical Oncology Meeting: Limited Activity Shown in Single-Agent Trials; Phase II Study of Omnitarg in Combination with Chemotherapy in Ovarian Cancer Currently Enrolling Patients; May 15, 2005. [cited 7/25/2012]. 'Available from:' http://www.gene.com/gene/news/press-releases/display.do?method=detail&id=8431&categoryid=4.

10. Kaye SB, Poole CJ, Danska-Bidzinska A, et al. A randomized phase II study evaluating the combination of carboplatin-based chemotherapy with pertuzumab versus carboplatin-based therapy alone in patients with relapsed, platinum-sensitive ovarian cancer. *Ann Oncol.* 2013;24(1):145-52. PMID: 23002282

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12. Meric-Bernstam F, Hurwitz H, Raghav KPS, et al. Pertuzumab plus trastuzumab for HER2-amplified metastatic colorectal cancer (MyPathway): an updated report from a multicentre, open-label, phase 2a, multiple basket study. *Lancet Oncol.* 2019;20(4):518-30. PMID: 30857956

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16. Phesgo (pertuzumab, trastuzumab, and hyaluronidase-zzxf) [package insert]. Genentech, Inc.; South San Francisco, CA; June 2020.

Revision History

Revision Date	Revision Summary
6/20/2024	• Add coverage criteria for patients with intolerance to Kadcyla (adjuvant use in breast cancer). • Clarification of criteria wording in Investigational Uses, to be explicit (no change to intent).
6/15/2023	No criteria changes with this annual update.
6/17/2022	Added colorectal cancer and non-small cell lung cancer as investigational uses. No criteria changes with this annual update.
7/16/2021	No criteria changes with this annual update.
1/20/2021	Added Phesgo (pertuzumab/trastuzumab/hyaluronidase) to policy.
7/22/2020	Reworded references to trastuzumab to be agnostic to brand name to account for upcoming changes in biosimilars policy (dru620).
.4/22/2020	• Added coverage criteria for adjuvant use for specific patients (node-positive, did not receive prior neoadjuvant therapy, and no prior HER2-directed chemotherapy). • Added COT criteria.
7/24/2019	Updated policy with standard language, including clarifying the Authorization Period to state 'until disease progression' (no change to policy intent) when used in the metastatic disease setting.
8/17/2018	• Adjuvant use of pertuzumab was moved from 'investigational' to 'not medically necessary'. • The "Administration, Quantity Limitations, and Authorization Period" section was updated say that pertuzumab should be discontinued when trastuzumab is discontinued (supports investigational position that pertuzumab is not covered as the sole HER2-blocking therapy).
10/13/2017	No criteria changes with this annual update
5/13/2016	For coverage of pertuzumab in the metastatic setting, made the clarification that the patient has had no prior treatment for HER2-positive metastatic BC. The prior criterion (I.A.2.a) stated, "Patient has had no prior therapy for metastatic breast cancer".

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Medication Policy Manual | **Policy No:** dru298

Topic: Kadcyla, ado-trastuzumab emtansine | **Date of Origin:** May 16, 2013

Committee Approval Date: June 20, 2024 | **Next Review Date:** 2025

Effective Date: September 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Kadcyla (ado-trastuzumab emtansine) is an antibody-drug conjugate (ADC) that is used to treat metastatic, HER2-positive breast cancer when the disease has progressed after standard therapy. It works by blocking HER2 receptors while delivering cytotoxic chemotherapy medication directly to cancer cells. It is administered as an intravenous infusion.

Policy/Criteria

Most contracts require pre-authorization approval of Kadcyla (ado-trastuzumab emtansine) prior to coverage.

I. Continuation of therapy (COT): Kadcyla (ado-trastuzumab emtansine) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Kadcyla (ado-trastuzumab emtansine) may be considered medically necessary in patients with breast cancer when there is clinical documentation (including, but not limited to chart notes) that criteria A and B below are met.

A. A diagnosis of **HER2-positive breast cancer**.

AND

B. Use in one of the following treatment settings (criterion 1 or 2):

1. **Metastatic disease:** When there is progression of disease after treatment with trastuzumab and a taxane (docetaxel or paclitaxel), when given either separately or in combination.

OR

2. **Non-metastatic disease (early disease)** when all of the following criteria are met (a, b, and c):

   a. There is documented residual invasive disease (tumor or lymph nodes) after surgery (Kadcyla [ado-trastuzumab emtansine] will be used in the ADJUVANT setting).

   AND

   b. At least six cycles (16 weeks) of neoadjuvant chemotherapy were administered prior to surgery.

   AND

   c. Neoadjuvant therapy (prior to surgery) included both of the following (i and ii):

      i. At least nine weeks of taxane therapy.

      AND

      ii. At least nine weeks of trastuzumab therapy.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Kadcyla (ado-trastuzumab emtansine) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Kadcyla (ado-trastuzumab emtansine) will be authorized as follows:

1. **Metastatic disease:** Authorization **may** be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement (including that there is no disease progression).

OR

2. **Non-metastatic disease (early disease):** Until disease progression, or up to a maximum of 14 cycles. No additional doses will be authorized.

IV. Kadcyla (ado-trastuzumab emtansine) is considered investigational when used in combination with Perjeta (pertuzumab).

V. Kadcyla (ado-trastuzumab emtansine) is considered investigational when used for all other conditions, including but not limited to:

A. HER2-positive breast cancer when trastuzumab has not been part of the prior treatment history.

B. HER2-negative breast cancer.

C. Gastric cancer.

D. HER2 mutations in non-small cell lung cancer.

Position Statement

- Kadcyla (ado-trastuzumab emtansine) is an antibody-drug conjugate that works via its blockade of HER2 receptors and delivery of cytotoxic chemotherapy to cancer cells.
- The intent of this policy is to cover Kadcyla (ado-trastuzumab emtansine) for the indications and dose for which it has been shown to be safe and effective, as detailed in the coverage criteria.
    * It was initially approved for use in the treatment of HER2-positive metastatic breast cancer (BC) in patients who have received a prior trastuzumab and taxane-based regimen for their metastatic disease, or when disease recurs during or within six months of completing adjuvant therapy with a trastuzumab and taxane-based regimen.
    * Subsequently, it was approved for use in HER2-positive non-metastatic (early) BC, as adjuvant therapy for residual invasive disease, after trastuzumab and taxane-based neoadjuvant therapy.
- Kadcyla (ado-trastuzumab emtansine) has only been evaluated when used as monotherapy. It should not be used in combination with trastuzumab, because it is duplication of therapy, or Perjeta (pertuzumab), where its safety and effectiveness have not been evaluated.
- Additionally, the safety and effectiveness of Kadcyla (ado-trastuzumab emtansine) have not been evaluated in other types of cancer.
- The most common side effects reported with Kadcyla (ado-trastuzumab emtansine) include fatigue, nausea, thrombocytopenia, headache, elevated liver enzymes, neuropathy, and constipation. Platelet count should be evaluated prior to each dose.
- Kadcyla (ado-trastuzumab emtansine) is given in a dose of 3.6 mg/kg via intravenous infusion over 90 minutes every 3 weeks until disease progression for metastatic disease and for up to 14 total cycles for residual disease in early BC.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.

- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy

METASTATIC BREAST CANCER

There is moderate certainty in the evidence that Kadcyla (ado-trastuzumab emtansine) improves survival in patients with HER2-positive metastatic breast cancer (mBC) relative to Tykerb (lapatinib) plus capecitabine.

- A large randomized, open-label, controlled trial compared Kadcyla (ado-trastuzumab emtansine) with Tykerb (lapatinib) plus capecitabine in patients with HER2-positive mBC. [1]
    * The study enrolled patients who had progression of their disease after therapy with trastuzumab and a taxane, either in the metastatic or adjuvant setting.
    * Progression-free survival (PFS) and overall survival were evaluated as co-primary endpoints.
    * There was a 6-month improvement in overall survival (OS) in favor of Kadcyla (ado-trastuzumab emtansine) based on an interim survival analysis. The study was stopped after statistical testing determined that a significant OS advantage would be maintained throughout the full planned duration of the study.
    * Any future survival analyses will be confounded because subjects were allowed to cross over to Kadcyla (ado-trastuzumab emtansine) after the interim survival analysis.
- Kadcyla (ado-trastuzumab emtansine) has not been compared with any other medication regimens commonly used in the second- and third-line HER2-positive mBC setting.
- There is a small (n = 137), proof-of-concept trial comparing Kadcyla (ado-trastuzumab emtansine) with trastuzumab plus docetaxel in the first-line (no prior trastuzumab) HER2-positive mBC setting. [2,3]
    * There is low confidence in the evidence from this study due to lack of detail regarding the proportion of subjects who withdrew from the comparator arm, the use of an endpoint (progression-free survival) that has not been correlated with clinically relevant outcomes, and lack of blinding.
    * Larger, well-controlled studies are needed to establish its safety and effectiveness in this treatment setting.
- There are no published clinical trials evaluating the combination of Kadcyla (ado-trastuzumab emtansine) and Perjeta (pertuzumab).
- The National Comprehensive Cancer Network (NCCN) breast cancer guideline recommends Kadcyla (ado-trastuzumab emtansine) for patients with HER2-positive mBC that have had prior exposure to trastuzumab-based regimens. It also has a recommendation as an adjuvant therapy in the resectable disease setting. [4]

NON- METASTATIC (EARLY) BREAST CANCER

There is low certainty in the evidence that adjuvant Kadcyla (ado-trastuzumab emtansine) improves survival in patients with HER2-positive non-metastatic BC relative to trastuzumab.

- A large randomized, open-label controlled trial compared Kadcyla (ado-trastuzumab emtansine) versus trastuzumab as adjuvant therapy in patients with HER2-positive non-metastatic BC and residual invasive disease after neoadjuvant therapy. [5]
    * The study enrolled patients who had residual invasive disease in the breast or axilla at surgery after neoadjuvant therapy with a taxane (with or without anthracycline) and trastuzumab.
    * All patients had at least 16 weeks of neoadjuvant therapy prior to surgery and at least nine weeks (three cycles) each of a taxane and trastuzumab.
    * Patients received a maximum of 14 cycles of Kadcyla (ado-trastuzumab emtansine).
    * Invasive disease-free survival (iDFS) was the primary endpoint. Overall survival was a secondary endpoint.
    * There was a reported invasive disease-free survival (iDFS) advantage with Kadcyla (ado-trastuzumab emtansine) [at 3 years, 88% vs. 77% with trastuzumab].
    * iDFS is a surrogate endpoint that has not been found to accurately predict benefit with regard to any clinically relevant outcome (e.g., overall survival (OS), quality or life). The effect of Kadcyla (ado-trastuzumab emtansine) on OS in this setting is unknown at this time.
- The NCCN breast cancer guideline recommends Kadcyla (ado-trastuzumab emtansine) for locally advanced, invasive, HER2-positive breast cancer after preoperative systemic therapy when residual disease is present. [4]

Use of Kadcyla (ado-trastuzumab emtansine) in other conditions

- Kadcyla (ado-trastuzumab emtansine) is also being studied in gastric cancer; however, there is insufficient evidence evaluating its efficacy in this condition. [6]
- Kadcyla (ado-trastuzumab emtansine) has not been studied in HER2-negative BC.
- Kadcyla (ado-trastuzumab emtansine) is also being studied in *ERBB2* (also known as HER2) mutations; however, there is insufficient evidence evaluating its efficacy in this condition. [4]

Safety [7]

- Commonly (incidence > 25%) adverse effects reported with Kadcyla (ado-trastuzumab emtansine) include fatigue, nausea, musculoskeletal pain, thrombocytopenia, headache, increased transaminases, and constipation.
- Kadcyla (ado-trastuzumab emtansine) labeling carries boxed warnings for hepatotoxicity, reduction in left ventricular ejection fraction (LVEF), and potential for fetal harm.

- Package labeling also carries warnings for pulmonary toxicity, hemorrhage, and peripheral neuropathy. Platelets should be monitored prior to each dose due to the potential for thrombocytopenia.

Dosing and administration [7]

- Kadcyla (ado-trastuzumab emtansine) is given in a dose of 3.6 mg/kg given intravenously over 90 minutes every 3 weeks (until progression in the metastatic setting or for up to 14 cycles as an adjuvant therapy for residual disease).
- Dose modification may be necessary for hepatotoxicity, decrease in LVEF, thrombocytopenia, pulmonary toxicity, or peripheral neuropathy.

Cross References
BlueCross BlueShield Association Medical Policy, 5.01.22 - Ado-Trastuzumab Emtansine (Trastuzumab-DM1) for Treatment of HER2-Positive Malignancies [August 2023]
Products with Therapeutically Equivalent Biosimilars/Reference Products, Medication Policy Manual, Policy No. dru620
Enhertu, fam-trastuzumab deruxtecan-nxki, Medication Policy Manual, Policy No. dru623
Nerlynx, neratinib, Medication Policy Manual, Policy No. dru520
pertuzumab-containing medications, Medication Policy Manual, Policy No. dru281
Tukysa, tucatinib, Medication Policy Manual, Policy No. dru646
lapatinib (generic, Tykerb), Medication Policy Manual, Policy No. dru145

Codes	**Number**	**Description**
HCPCS	J9354	Injection, ado-trastuzumab emtansine (Kadcyla), 1 mg

References

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Revision History

Revision Date	Revision Summary
6/20/2024	No criteria changes with this annual review.
6/15/2023	There were no changes to the coverage criteria with this annual update.
6/17/2022	There were no changes to the coverage criteria with this annual update. *Note: Revisions were made to update to current standard policy language; however, there was no change to the intent of this policy.*
7/16/2021	Updated continuation of therapy criteria. Added HER2 mutations in non-small cell lung cancer as an investigational use. No other changes with this annual update.
7/22/2020	Added continuation of therapy (COT) criteria. Removed references to brand Herceptin to account for upcoming changes to biosimilar policy (dru620). No other changes with this annual update.
7/24/2019	Add coverage criteria for non-metastatic breast cancer, for use in the adjuvant setting, based on new evidence and indication (effective 8/15/2019).
10/19/2018	Updated policy with standard language, including clarifying the Authorization Period to state 'until disease progression' (no change to policy intent)
10/13/2017	No criteria changes with this annual update
5/13/2016	No changes to coverage criteria with this annual update

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Medication Policy Manual

Policy No: dru310

Topic: Abraxane, nab-paclitaxel (a.k.a. albumin-bound paclitaxel, paclitaxel albumin-stabilized nanoparticle formulation, ABI-007)

Date of Origin: July 12, 2013

Committee Approval Date: December 7, 2023

Next Review Date: 2024

Effective Date: March 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Abraxane (nab-paclitaxel) is a protein-bound form of paclitaxel (generic Taxol). It is an intravenous taxane chemotherapy medication used in the treatment of certain cancers.

PLEASE NOTE: This policy and the coverage criteria below do not apply to paclitaxel (generic Taxol). Generic paclitaxel (Taxol) does not require pre-authorization.

Policy/Criteria

Most contracts require pre-authorization approval of Abraxane (nab-paclitaxel) prior to coverage.

I. Continuation of therapy (COT): Abraxane (nab-paclitaxel) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Abraxane (nab-paclitaxel) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criterion A, B, or C below is met.

A. A diagnosis of **cancer where paclitaxel is indicated** and criterion 1 or 2 below is met.

1. Previous treatment with paclitaxel or docetaxel was not tolerated due to a documented hypersensitivity reaction, despite use of recommended premedications.

OR

2. There is a medical contraindication to recommended pre-medications (corticosteroids, diphenhydramine, and H2 antagonists for paclitaxel; corticosteroids for docetaxel) such that use of paclitaxel or docetaxel is contraindicated.

OR

B. A diagnosis of recurrent or refractory **metastatic breast cancer (MBC)** and treatment with an anthracycline-based chemotherapy regimen has been ineffective, contraindicated, or not tolerated. (see *Appendix 1*)

OR

C. A diagnosis of locally advanced or metastatic **pancreatic cancer** when given in combination with gemcitabine.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Abraxane (nab-paclitaxel) coverable only under the medical benefit (as a provider-administered medication).

B. Authorization may be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

IV. Abraxane (nab-paclitaxel) is considered not medically necessary (unless generic paclitaxel products were not tolerated due to hypersensitivity, despite use of pre-medications) when used for:

A. First-line treatment of non-small cell lung cancer (NSCLC)

B. First-line treatment of breast cancer (any stage)

V. Abraxane (nab-paclitaxel) is considered investigational when used for all other conditions, including but not limited to treatment of the following, unless generic paclitaxel products were not tolerated due to hypersensitivity:

A. Colorectal cancer.

B. Prostate cancer.

C. Uterine sarcoma.

Position Statement

- Abraxane (nab-paclitaxel) is paclitaxel (generic Taxol), a microtubule inhibitor, bound to a protein. It is approved for use in the treatment of metastatic breast cancer when front-line therapies are not effective, in the front-line treatment of metastatic pancreatic cancer when used in combination with gemcitabine, and for advanced non-small cell lung cancer (NSCLC) as a first-line therapy when used in combination with carboplatin.
- Generic taxanes, including docetaxel and paclitaxel, are effective in the treatment of many patients with a variety of cancers including, but not limited to, lung, ovarian and breast cancers.
- For recurrent or refractory metastatic breast cancer, Abraxane (nab-paclitaxel) is one of many effective single-agent options (*see Appendix 1*).

- Abraxane (nab-paclitaxel) has not been proven to be safer or more effective than generic paclitaxel for advanced or metastatic NSCLC. Abraxane (nab-paclitaxel) is among several options (see *Appendix 2*) that may be used first-line to treat advanced or metastatic NSCLC.
- For metastatic pancreatic cancer, the addition of Abraxane (nab-paclitaxel) to gemcitabine improves overall survival over gemcitabine alone.
- Because Abraxane (nab-paclitaxel) is a unique formulation of paclitaxel, there is interest in using it in other indications where standard generic paclitaxel has been shown to be effective. There is currently no reliable evidence supporting superior efficacy of Abraxane (nab-paclitaxel) over generic paclitaxel or other taxanes (docetaxel); however, it is much more costly.
- There is no reliable evidence to allow conclusion that Abraxane (nab-paclitaxel) is safer than generic paclitaxel.
    * Like generic paclitaxel, Abraxane (nab-paclitaxel) is also associated with significant adverse effects including myelosuppression (boxed warning for neutropenia), sensory neuropathy, alopecia, nausea/vomiting, and hypersensitivity.
    * Solvents in generic paclitaxel (Cremophor) may be associated with infusion-related side effects; pre-medication with corticosteroids, diphenhydramine, and H2 antagonists is used to minimize infusion reactions. Although Abraxane (nab-paclitaxel) does not require pre-medication, it also can cause hypersensitivity reactions.
    * Solvents in generic docetaxel (polysorbate 80) can also cause hypersensitivity reactions. Premedication with dexamethasone is recommended.
- Abraxane (nab-paclitaxel) is currently being studied in many other types of cancers; however, the current state of the evidence is insufficient to support a clinical benefit in these populations.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.

- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy

BREAST CANCER

Recurrent or refractory

- Abraxane (nab-paclitaxel) has not been proven in high quality clinical studies to be more effective than alternative treatment options for recurrent or refractory metastatic breast cancer (MBC). Of note, the doses of paclitaxel, given as Abraxane (nab-paclitaxel), were significantly higher in the comparative trials than the generic paclitaxel doses, yet Abraxane (nab-paclitaxel) failed to produce consistently superior survival.
- One low quality randomized non inferiority trial reported Abraxane (nab-paclitaxel) to be as effective as paclitaxel for MBC, based on overall response rate. There was a trend towards superior overall survival; however, the trial was not powered for overall superiority. A subset analysis found overall survival was superior with Abraxane (nab-paclitaxel) in previously treated women (refractory or recurrent MBC), but not in patients being treated in the first-line setting. [1] As a result, the FDA approved nab-paclitaxel (Abraxane) for use only in the refractory or recurrent metastatic setting. [2]
    * Significant flaws that impacted the certainty of the results included use of an open-label design and an endpoint with subjective components (overall response rate).
    * In addition, use of an open-label design also confounds reliability of overall survival results, as well as use of subsequent, post-protocol chemotherapy.

First-line:

- There is insufficient evidence to support the use of Abraxane (nab-paclitaxel) over generic taxanes for the first-line treatment of MBC. Studies are limited to one phase 2 trial versus docetaxel, [3,4] along with the Phase 3 trial, which failed to show superior overall survival versus generic paclitaxel. [1]
- There is insufficient evidence to support the use of Abraxane (nab-paclitaxel) for earlier stage (non-metastatic) breast cancer. One Phase 3 trial evaluated Abraxane (nab-paclitaxel) vs. paclitaxel for primary invasive breast cancer. Pathological complete response (PCR), the primary outcome, was higher with Abraxane (nab-paclitaxel) than with paclitaxel (38% vs. 29%). Despite a statistically significant difference in PCR, it is unknown if this difference in PCR will translate in to improved overall survival, the most meaningful health outcome for breast cancer. [23]
- Because there is no evidence of superiority for overall survival with Abraxane (nab-paclitaxel) and there are many alternatives that provide a better value, the use of Abraxane (nab-paclitaxel) for first-line breast cancer (any stage) is considered not medically necessary.

NCCN guidelines

- The current National Comprehensive Cancer Network (NCCN) breast cancer guideline lists Abraxane (nab-paclitaxel) among many possible "other" single-agent treatment options for recurrent or metastatic breast cancer. Preferred single-agent options include but are not limited to taxanes (paclitaxel), anthracyclines (doxorubicin HCl, doxorubicin liposomal), anti-metabolites (gemcitabine, capecitabine) and microtubule inhibitors (vinorelbine, eribulin). See *Appendix 1* for "Other" single-agent options. The NCCN does not specifically recognize use of Abraxane (nab-paclitaxel) for early stage (non-metastatic/non-recurrent) breast cancer. [5]

PANCREATIC CANCER:

- In the first-line treatment of metastatic pancreatic cancer, the addition of Abraxane (nab-paclitaxel) to gemcitabine improves overall survival over gemcitabine alone (8.5 versus 6.7 months), based on one large Phase 3 trial (n=861). [6,7]
- Abraxane (nab-paclitaxel) plus gemcitabine is a NCCN preferred, category 2A recommended option for locally advanced pancreatic cancer and a preferred, category 1 recommendation for metastatic pancreatic cancer. [6]

NON-SMALL CELL LUNG CANCER (NSCLC):

- One randomized, controlled study compared Abraxane (nab-paclitaxel) to generic paclitaxel for advanced and metastatic NSCLC. Despite a higher overall response rate with Abraxane (nab-paclitaxel) (33% versus 25%), the primary endpoint, the study failed to demonstrate any statistically significant difference between the two treatments for overall survival (12.1 months versus 11.2 months, p=0.271). Both progression free survival and overall survival were secondary endpoints and part of the non-inferiority analysis. [8]
- The current NCCN guideline lists Abraxane (nab-paclitaxel) among many possible platin-doublet treatment options for first-line treatment of NSCLC, in combination with cisplatin or carboplatin. Other platin-doublet options include but are not limited to cisplatin or carboplatin plus generic taxanes (paclitaxel, docetaxel), anti-metabolites (gemcitabine, pemetrexed), microtubule inhibitors (vinblastine, vinorelbine) and etoposide, as well as non-platin doublets (gemcitabine/docetaxel or gemcitabine/vinorelbine). [9]
- Because there is no evidence of superiority for overall survival and there are many alternatives that provide a better value, the use of Abraxane (nab-paclitaxel) for first-line NSCLC is considered not medically necessary.

Use in Other Conditions

OVARIAN CANCER:

- No single therapy is preferred for treatment of recurrent ovarian cancer based on the current NCCN ovarian cancer guideline. [10]
- For platinum-sensitive disease, carboplatin combinations with paclitaxel (Category 1), docetaxel or gemcitabine are preferred. Abraxane (nab-paclitaxel) is listed as one of many single-agent options for platinum-sensitive recurrent disease (category 2A).
- The evidence for the use of single-agent Abraxane (nab-paclitaxel) in recurrent platinum-sensitive ovarian cancer is limited to one small Phase 2 trial. [11]

- Abraxane (nab-paclitaxel) has not been studied in paclitaxel-resistant disease.
- More trials are needed to evaluate the place of Abraxane (nab-paclitaxel) in ovarian cancer therapy.

COLORECTAL CANCER, PROSTATE CANCER, AND UTERINE SARCOMA

- Several small studies have evaluated Abraxane (nab-paclitaxel) in colorectal cancer [27], and prostate cancer [13]. However, no promising activity was shown in these cancers.
- No published clinical trials evaluating generic paclitaxel or nab-paclitaxel (Abraxane) in uterine sarcoma were identified in researching this policy.
- Generic paclitaxel or Abraxane (nab-paclitaxel) are not part of the standard of care for any of these cancers based on current NCCN guidelines. [19]

OTHER CANCERS

- Generic paclitaxel is part of the treatment paradigm for several other cancers including, but not limit to, endometrial, esophageal junction, head and neck squamous cell cancer (HNSCC), urothelial, and cutaneous melanoma. [19] Although Abraxane (nab-paclitaxel) has also been used in several of these settings, it has not been shown to be safer or more effective than generic paclitaxel. [12, 14-17]
- In some cancers, such as cutaneous melanoma, immune checkpoint inhibitor therapies and targeted therapies have eclipsed the use of chemotherapy agents like generic paclitaxel and Abraxane (nab-paclitaxel) as they are associated with better outcomes (e.g., improved overall survival).
- Biliary tract cancers (BTC), including cholangiocarcinoma (CCA):
    * There are two small, uncontrolled trials evaluating Abraxane (nab-paclitaxel) in biliary tract cancers (BTC), including cholangiocarcinoma (CCA) when used in combination with gemcitabine or gemcitabine plus cisplatin. One study did not meet its primary endpoint. [24] The other study suggested potential activity with this combination relative to a historical cohort. [25]
    * A subsequent unpublished phase 3 study (SWOG 1815) of patients with newly-diagnosed, advanced biliary tract cancers (n=441) did not find a statistical improvement in median overall survival with the addition of albumin-bound paclitaxel (Abraxane) (GAP) to the standard of care gemcitabine/cisplatin (GC). [27]
        - 67% of patients had intrahepatic CCA, 16% had gallbladder adenocarcinoma [GBC], and 17% had extrahepatic CCA. Most pts had metastases (73%).
        - Median OS was 14 months with GAP vs. 12.7 months with GC (p=0.58). In addition, GAP was associated with a higher rate of adverse events, including hematologic adverse events.
        - Exploratory analyses of locally advanced disease and GBC favored use of GAP; however, the analyses were not powered for conclusion of superiority.
        - Further analyses are ongoing and additional trials are needed to establish the safety and efficacy of Abraxane in this clinical setting.
    * There is no evidence for the use of albumin-bound paclitaxel (Abraxane) in resectable BTC.

    * There are several other potential chemotherapy regimens recommended by the NCCN in this treatment setting. [26]
- The NCCN recognizes the use of generic paclitaxel for a variety of cancers, including bladder, breast, cervical, esophageal, gastric, head and neck (SCCHN), kidney, lung, ovarian, penile, testicular, uterine, endometrial, and thyroid cancers; melanoma, unspecified adenocarcinoma, thymoma, and angiosarcoma. [19]

Safety

- There is no reliable evidence to allow conclusion that Abraxane (nab-paclitaxel) is safer than generic paclitaxel.
- Generic paclitaxel contains solvents, such as Cremophor, that dissolve the paclitaxel and may be associated with infusion-related hypersensitivity requiring premedication with corticosteroids, diphenhydramine and H2-receptor antagonists. [19]
- Abraxane (nab-paclitaxel) formulation does not contain solvents and may be an option for patients with hypersensitivity to generic paclitaxel. Of note, use of nab-paclitaxel (Abraxane) has not been studied in patients with severe hypersensitivity reactions to generic paclitaxel. [9] Likewise, Abraxane (nab-paclitaxel) may be an option in patients with hypersensitivity to generic docetaxel.
- Although Abraxane (nab-paclitaxel) does not require pre-medication, it can cause hypersensitivity reactions. [2]
- Although both docetaxel (generic Taxotere) and paclitaxel (generic Taxol) are both "taxanes," they have different side effects. Namely, paclitaxel (generic Taxol) contains the solvent Cremophor which is associated with infusion-related hypersensitivity reactions with paclitaxel. Giving pre-medications (e.g. steroids, diphenhydramine, and ranitidine) can help minimize these infusion reactions. [19]
- Infusion-related reactions, which happen at the time of the infusion, can be seen with docetaxel (generic Taxotere), as it contains polysorbate 80, another diluent known to cause infusion reactions. Pre-medication with dexamethasone is recommended prior to infusion of docetaxel. [19]
- An allergic reaction to docetaxel aside from during an infusion generally is considered a reaction to the docetaxel and not the diluent. Generally, use of another taxane would be relatively contraindicated.
- Neuropathy can be a dose-limiting side effect of either generic paclitaxel or nab-paclitaxel (Abraxane); however, neuropathy is not considered a hypersensitivity reaction. In addition, there is no conclusive evidence that the incidence of neuropathy is lower with Abraxane (nab-paclitaxel) than with generic paclitaxel. [20] A study in patients with breast cancer found a similar incidence of neuropathy with generic paclitaxel and Abraxane (nab-paclitaxel). [21] A recent review of the use of Abraxane (nab-paclitaxel) in patients with non-small cell lung cancer showed less grade four neuropathy, compared to generic paclitaxel, but the incidence of neuropathy overall was about the same. [22]
- The most common adverse reactions (>20%) reported with Abraxane (nab-paclitaxel) include alopecia, blood dyscrasias (anemia, neutropenia, thrombocytopenia), sensory neuropathy, abnormal ECG, fatigue/asthenia, myalgia/arthralgia, liver function test

abnormalities (AST/alkaline phosphatase elevation), GI disturbance (nausea, diarrhea), infections. [2]

- Like generic paclitaxel, Abraxane (nab-paclitaxel) carries a Boxed Warning for neutropenia. [2,17]

Appendix 1: Chemotherapy Agents Used in the Treatment of Metastatic Breast Cancer [5] [a]	
Preferred Single Agents	***Chemotherapy Combinations***
Anthracyclines	AC: doxorubicin/cyclophosphamide
doxorubicin (generic Adriamycin)	EC: epirubicin/cyclophosphamide
Doxorubicin, liposomal (Doxil)	CMF: cyclophosphamide/methotrexate/fluorouracil
Taxanes	docetaxel/capecitabine (generic Xeloda)
paclitaxel (generic Taxol)	GT: gemcitabine/paclitaxel
Anti-metabolites	gemcitabine/carboplatin
capecitabine (generic Xeloda)	paclitaxel/bevacizumab
gemcitabine (generic Gemzar)	carboplatin/paclitaxel OR nab-paclitaxel (Abraxane)
Other microtubule inhibitors	
vinorelbine (generic Navelbine)	
eribulin (generic Halaven	
Other Single Agents	***Agents Targeted for HER-2 positive disease*** [b]
cyclophosphamide (generic Cytoxan)	Perjeta (pertuzumab) [c]
carboplatin	trastuzumab
docetaxel	Kadcyla (ado- trastuzumab)
Abraxane (nab-paclitaxel)	Tykerb (lapatinib)
cisplatin	Tukysa (tucatinib)/trastuzumab/capecitabine [cat 1]
epirubicin	Enhertu (fam-trastuzumab deruxtecan)
Ixempra (ixabepilone)	Nerlynx (neratinib)

[a] All are NCCN 2A recommendations, except as noted

[b] Most agents for HER-2 positive disease are used in combination with cytotoxic chemotherapy (e.g. docetaxel, paclitaxel, carboplatin, capecitabine, vinorelbine).

[c] Category 1, with trastuzumab and docetaxel.

Appendix 2: Cytotoxic Chemotherapy Agents Used in the First-line Treatment of Non-small Cell Lung Cancer [9] [a]	
PD-1/PD-L1 inhibitors	
Keytruda (pembrolizumab) +	Alimta (pemetrexed) + cisplatin or carboplatin (preferred)
Tecentriq (atezolizumab) +	carboplatin/paclitaxel/bevacizumab carboplatin/Abraxane(nab-paclitaxel) [category 2A]
Opdivo (nivolumab) +	Yervoy (ipilimumab) Yervoy (ipilimumab) + Alimta (pemetrexed) + carboplatin/cisplatin
Platin-doublets	
cisplatin or carboplatin +	docetaxel, etoposide, gemcitabine, paclitaxel, Abraxane (nab-paclitaxel), Alimta (pemetrexed)
Other doublet therapies:	
gemcitabine **+** docetaxel or vinorelbine	
Doublet chemotherapy plus bevacizumab	
carboplatin **+** paclitaxel **+** bevacizumab carboplatin or cisplatin + Alimta (pemetrexed) + bevacizumab [category 2A]	

[a] All are NCCN Category 1 recommendations, except as noted. This list includes most but not all regimens (for reference).

Appendix 3: Lung cancer histological subtypes (and approximate incidence, %)
Lung cancer (162.0, 162.2-162.5, 162.8, 162.9)
A. Non-small cell lung cancer (NSCLC) (85-90%)
1) Squamous cell (epidermoid) carcinoma (25-30%)
2) Non-squamous cell (55%)
- Adenocarcinoma (40%)
- Large cell (undifferentiated) carcinoma (10-15%)
- Other
B. Small cell lung cancer (SCLC) (10-15%)
C. Unspecified lung cancer (< 5%)
American Cancer Society. What is non-small cell lung cancer?;16Dec2010. Available at: http://www.cancer.org/Cancer/LungCancer-Non-SmallCell/DetailedGuide/non-small-cell-lung-cancer-what-is-non-small-cell-lung-cancer

Codes	Number	Description
HCPCS	J9264	Paclitaxel protein-bound particles, (Abraxane) 1 mg IV

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Revision History

Revision Date	Revision Summary
12/7/2023	No criteria changes with this annual review.
12/9/2022	• Updated standard language in policy. • No changes to coverage criteria with this annual update.
1/20/2021	• Removed the following diagnoses from the 'Investigational' list in criterion V. so use in these conditions could be adjudicated using criterion A. (solvent-based hypersensitivity reaction to generic paclitaxel or when required pre-medications are contraindicated): endometrial cancer, gastroesophageal cancer, squamous cell cancer of the head and neck, ovarian cancer, and cholangiocarcinoma. • Updated continuation of therapy (COT) language.
6/15/2020	Removed references to brand Avastin and brand Herceptin from policy, to account for upcoming changes in biosimilars policy (dru620).
1/22/2020	• Added continuation of therapy (COT) criteria (no change to intent of coverage criteria). • Cholangiocarcinoma was added to investigational uses.
1/31/2019	There were no changes to coverage criteria with this annual update. Clarified documentation requirements (no change to intent).
2/16/2018	No change to intent of coverage criteria with this annual update.
2/17/2017	Add coverage criteria for docetaxel hypersensitivity reaction.
2/12/2016	Added to investigational uses: endometrial cancer, uterine sarcoma.
7/12/2013	New policy.

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Medication Policy Manual | **Policy No:** dru327

Topic: Gazyva, obinutuzumab | **Date of Origin:** January 17, 2014

Committee Review Date: March 6, 2025 | **Next Review Date:** 2026

Effective Date: May 1, 2025

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Gazyva (obinutuzumab) is an intravenous (IV) humanized monoclonal antibody. It is used in the treatment of chronic lymphocytic leukemia (CLL), and follicular lymphoma (FL), when administered with chemotherapy.

Policy/Criteria

Most contracts require pre-authorization approval of Gazyva (obinutuzumab) prior to coverage.

I. Continuation of therapy (COT): Gazyva (obinutuzumab) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Gazyva (obinutuzumab) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criterion A, B or C below is met.

A. Diagnosis of **chronic lymphocytic leukemia** (CLL) when criteria 1 and 2 below are met:

1. Gazyva (obinutuzumab) will be administered in combination with one of the following (a, b, or c):

a. Chlorambucil.

OR

b. Venclexta (venetoclax).

OR

c. Calquence (acalabrutinib).

AND

2. The patient has had no prior medication therapy for CLL.

OR

B. Diagnosis of **relapsed or refractory follicular lymphoma** (FL) when criteria 1 and 2 below are met:

1. Documentation of disease progression on or after a rituximab-containing regimen.

AND

2. Gazyva (obinutuzumab) will be administered in combination with bendamustine for six cycles, followed by Gazyva (obinutuzumab) monotherapy.

OR

C. Gazyva (obinutuzumab) is used as a one-time dose prior to initiation of therapy with Columvi (glofitamab) to deplete circulating and lymphoid tissue B cells.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Gazyva (obinutuzumab) coverable only under the medical benefit (as a provider-administered medication).

B. When preauthorization is approved, Gazyva (obinutuzumab) will be authorized as follows:

1. **CLL**: A single treatment course of up to eight 1,000-mg infusions in a 12-month period. No additional treatment courses will be authorized.

2. **FL**: Up to eight 1,000-mg infusions in the initial 6-month period when administered with bendamustine. After the initial 6-month period, up to six 1,000-mg infusions in a 12-month period as monotherapy for a maximum of 24 months of maintenance therapy. Note: there is a lifetime maximum of 30 months of treatment (twenty 1,000-mg infusions).

3. **Prior to Columvi (glofitamab) therapy**: Coverage will be provided for a single dose of 1,000 mg. No additional doses will be authorized.

C. Authorization **may** be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

IV. Gazyva (obinutuzumab) is considered not medically necessary when used for:

A. Untreated follicular lymphoma (FL) [first-line setting].

B. Relapsed/refractory FL, in combination with Brukinsa (zanubrutinib).

V. Gazyva (obinutuzumab) is considered investigational when used for all other conditions.

Position Statement

- Gazyva (obinutuzumab), an anti-CD20 humanized monoclonal antibody, is a B-cell-directed immunotherapy used in combination with chlorambucil for the treatment of chronic lymphocytic leukemia (CLL), in combination with bendamustine for the treatment of relapsed or refractory follicular lymphoma (FL), or in combination with chemotherapy for previously untreated stage II bulky, III, or IV FL.
- The intent of this policy is to allow coverage in the settings with proven benefit. The use of Gazyva (obinutuzumab) is considered 'not medically necessary' for uses with no proven benefit over less-costly alternatives.
- Gazyva (obinutuzumab) for CLL and FL is coverable for a finite treatment course, as detailed in the coverage criteria. The safety and effectiveness of additional treatment courses has not been studied.

Chronic Lymphocytic Leukemia

- Gazyva (obinutuzumab) was studied in patients who had no previous therapy for their CLL, and who were not candidates for more aggressive chemotherapy due to advanced age and/or comorbid conditions.
- FDA approval was based on improved progression-free survival (PFS) in patients who received chlorambucil plus Gazyva (obinutuzumab) versus those who received chlorambucil alone. There is currently no mature overall survival data available. Subsequently, the FDA approved use of Venclexta (venetoclax) in combination with Gazyva (obinutuzumab), based on improvement in PFS as compared to chlorambucil plus Gazyva (obinutuzumab).
- Gazyva (obinutuzumab) for CLL consists of a finite treatment course, as detailed in the coverage criteria. The safety and effectiveness of additional treatment courses has not been studied.
- National Comprehensive Cancer Network (NCCN) CLL/Small Lymphocytic Lymphoma (SLL) guideline lists Gazyva (obinutuzumab) as a treatment option for CLL and SLL.

Relapsed or Refractory Follicular Lymphoma (FL)

- Gazyva (obinutuzumab) was studied in patients with FL who had no response to or progressed on a rituximab-containing regimen.
- FDA approval in relapsed or refractory (r/r) FL was based on PFS in patients who received bendamustine plus Gazyva (obinutuzumab) versus bendamustine alone. There is currently no mature overall survival data available, nor is there any evidence that it improves any clinically relevant outcome such as symptom control or improved quality of life.
- More recently, the FDA approved the use of Brukinsa (zanubrutinib) for r/r FL, in combination with Gazyva (obinutuzumab). However, there is no proven efficacy or safety benefit of Brukinsa (zanubrutinib) with Gazyva (obinutuzumab) over lower cost regimens, including other Gazyva (obinutuzumab)-based regimens. Therefore, the use of Gazyva (obinutuzumab) with Brukinsa (zanubrutinib) for r/r FL is considered not medically necessary.
- The NCCN lists Gazyva (obinutuzumab) plus chemotherapy among several preferred, treatment option for relapsed or refractory FL. Potential third-line treatment options

include Gazyva (obinutuzumab) with Brukinsa (zanubrutinib), as well as the many available second-line treatment options which are listed as potential third-line treatment options if not previously used.

Previously Untreated Follicular Lymphoma (first-line)

- Gazyva (obinutuzumab) was also studied in patients with previously untreated stage II bulky (tumor ≥ 7 cm), III, or IV FL when given in combination with chemotherapy. It was compared with rituximab plus chemotherapy.
- There was a small advantage in PFS at three years; however, there was no difference in three-year survival. This study does not establish any clinically relevant difference between these two therapies.
- Rituximab-based regimens are the standard of care in treating FL, and are generally more cost effective than Gazyva (obinutuzumab)-based regimens.
- Because there is no proven efficacy or safety benefit of Gazyva (obinutuzumab)-based regimens over lower cost rituximab- based regimens, the use of Gazyva (obinutuzumab) in the first-line setting for FL is considered not medically necessary.

Use as a premedication prior to Columvi (glofitamab) therapy:

- A study evaluating Columvi (glofitamab) used a single dose of Gazyva (obinutuzumab) prior to initiating therapy with Columvi (glofitamab) to deplete circulating and lymphoid tissue B cells to reduce the incidence and severity of cytokine release syndrome (CRS).

Safety

- There is a high potential for off-label use of Gazyva (obinutuzumab) in B-cell-mediated diseases other than CLL and FL; however, there is no evidence supporting its safety and efficacy in these settings.
- Gazyva (obinutuzumab), as well as all anti-CD20 monoclonal antibodies, carries a boxed warning describing a risk for hepatitis B virus reactivation and for progressive multifocal leukoencephalopathy (PML).
- Infusion reactions are common and may be severe. Premedication is recommended. The first dose should be administered slowly and divided over two days.
- Other common adverse effects include bone marrow suppression, fever, cough, and musculoskeletal disorder.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations

are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.

- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy

Chronic Lymphocytic Leukemia

- There is a single, low-quality, unpublished, open-label, randomized controlled trial evaluating Gazyva (obinutuzumab) in combination with chlorambucil as a first-line therapy for certain patients with chronic lymphocytic leukemia (CLL). [1 2]
    - * Patients enrolled in the trial had confirmed B-cell CLL, had no prior medication treatment for their disease, and were not candidates for more aggressive chemotherapy due to comorbid conditions (e.g. reduced renal function).
    - * The primary endpoint in the study was investigator-reported progression-free survival (PFS). Overall survival (OS) will be reported as a secondary endpoint. PFS has not been validated as an accurate predictor of OS in this setting. [3]
    - * The study was completed in two stages. Stage 1 of the trial compared chlorambucil plus Gazyva (obinutuzumab) with chlorambucil alone. Stage 2 of the trial compared chlorambucil plus Gazyva (obinutuzumab) with chlorambucil plus rituximab.
    - * The Gazyva (obinutuzumab) treatment arm was reported to have a 12-month PFS advantage over chlorambucil alone (23 months and 11 months, respectively).
    - * In stage 2 of the trial, the Gazyva (obinutuzumab) treatment arm was reported to have an 11.5-month PFS advantage over the rituximab treatment arm (26.7 months and 15.2 months, respectively). [4 5] OS data from this trial is not mature at this time.
    - * Evidence from the trial was appraised as being of low quality due to the open-label design or the study and the high rate of attrition.
- A subsequent phase 3 trial compared Venclexta (venetoclax) plus Gazyva (obinutuzumab) versus chlorambucil plus Gazyva (obinutuzumab). The combination with venetoclax was numerically superior to chlorambucil for PFS (88.2% vs. 64% at 24 months). However, all-cause mortality was higher in the venetoclax group (9.3% vs. 7.9% with chlorambucil). [6 7]
- The evidence of efficacy for Gazyva (obinutuzumab) in combination with Calquence (acalabrutinib) in the front-line CLL setting is based on one phase III, open-label trial; ELEVATE-TN. This trial evaluated progression free survival (PFS) as the primary endpoint, and overall response rate (ORR) as a secondary endpoint. [8]
    - * Patients with treatment-naïve CLL were randomized to receive acalabrutinib monotherapy, acalabrutinib with obinutuzumab, or chlorambucil with obinutuzumab.

    - At median follow-up of 28.3 months, median PFS was longer with acalabrutinib-obinutuzumab (NR) and acalabrutinib monotherapy (NR), compared with obinutuzumab-chlorambucil (22.6 months). In addition, Treatment with acalabrutinib-obinutuzumab, acalabrutinib, and obinutuzumab-chlorambucil led to an overall response rate (ORR) of 94%, 86%, and 79%, respectively.
    - This trial was not designed nor powered to assess the benefit of acalabrutinib monotherapy versus acalabrutinib-obinutuzumab.
- Gazyva (obinutuzumab) has not been studied in the relapsed or refractory CLL setting, or when used as a single agent for CLL.
- NCCN lists Gazyva (obinutuzumab) as a treatment option when used as monotherapy for relapsed or refractory CLL/SLL. Gazyva (obinutuzumab) in combination with Venclexta (venetoclax) or Calquence (acalabrutinib) is listed as a preferred treatment regimen in the first-line CLL setting in patients without del(17p)/TP53 mutation as well as in the first-line CLL setting in patients with a del(17p)/TP53 mutation. [9]

Follicular lymphoma

- There is a low-quality, unpublished, open-label, randomized controlled (RCT) trial [GADOLIN] evaluating Gazyva (obinutuzumab) in combination with bendamustine as a therapy for patients with relapsed or refractory (r/r) indolent non-Hodgkin lymphomas (NHLs) who had no response or progressed on a rituximab-containing regimen, The vast majority of the subjects enrolled in the trial had follicular lymphoma (FL). [2 10] Results reported below are for the cohort with FL (N = 321).
    - Patients were randomized to receive either Gazyva (obinutuzumab) plus bendamustine or bendamustine alone. Patients who received Gazyva (obinutuzumab) plus bendamustine and did not have disease progression at the end of 6 months continued receiving Gazyva (obinutuzumab) monotherapy for up to 2 years.
    - The median PFS of the Gazyva (obinutuzumab) plus bendamustine arm has not been reached, although it is estimated to be 29.2 months. The reported median PFS of the bendamustine alone arm is 13.8 months.
    - The median OS has not been reached in either arm after about 45 months.
- A second open-label, RCT compared Gazyva (obinutuzumab) plus chemotherapy with rituximab plus chemotherapy as a front-line regimen in patients with CD20-positive indolent non-Hodgkin's lymphoma [GALLIUM]. [2 11]
    - Patients in the FL cohort had stage II bulky, stage III, or stage IV disease, and had no prior systemic therapy for their disease.
    - Those achieving at least a partial response after initial combination therapy were continued on monotherapy with the assigned monoclonal antibody therapy.
    - The three-year PFS was 81.9% and 77.9% in the Gazyva (obinutuzumab) and rituximab treatment arms, respectively [HR 0.71; 95% CI 0.54, 0.93; p = 0.01]. Median PFS was not reached in either group.
    - There was no difference between groups in 3-year OS. Median OS was not reached in either group.

- More recently, the FDA approved the use of Brukinsa (zanubrutinib) for r/r FL, in combination with Gazyva (obinutuzumab), after two or more lines of systemic therapy, based on unpublished results (abstract) of a phase 2 trial comparing the combination regimen with Gazyva (obinutuzumab) monotherapy [ROSEWOOD].[12 13] However, there is no proven efficacy or safety benefit of Brukinsa (zanubrutinib) with Gazyva (obinutuzumab) over lower cost regimens, including other Gazyva (obinutuzumab)-based regimens. Therefore, the use of Gazyva (obinutuzumab) with Brukinsa (zanubrutinib) for r/r FL is considered not medically necessary.
    * All patients in the trial received ≥2 previous systemic therapies for FL (including an anti-CD20 antibody and an alkylating agent). About half of enrolled patients were refractory to rituximab.
    * Based on details from the unpublished abstract, overall response rate (ORR) was higher with combination therapy as compared to monotherapy (69% vs. 46%). However, a large portion (49%) of patients crossed over from monotherapy to the combination arm, such that the results are confounded and interpretation of any benefit of one treatment arm over the other is uncertain.
    * In addition, Brukinsa (zanubrutinib) with Gazyva (obinutuzumab) has not been compared to any pf the many other lower cost regimens, including other Gazyva (obinutuzumab)-based regimens. Therefore, the use of Gazyva (obinutuzumab) with Brukinsa (zanubrutinib) for r/r FL is considered not medically necessary.
- The NCCN lists Gazyva (obinutuzumab) plus chemotherapy among several preferred, treatment options for relapsed or refractory FL. Potential third-line treatment options include Gazyva (obinutuzumab) with Brukinsa (zanubrutinib), as well as the many available second-line treatment options which are listed as potential third-line treatment options if not previously used. Choice of third-line therapy is dependent on prior lines of treatment, which may include autologous hematopoietic stem cell rescue. For front-line treatment, the guideline lists both Gazyva (obinutuzumab) plus chemotherapy and rituximab plus chemotherapy as preferred, treatment options. [9]

Investigational conditions

- Although the GADOLIN study enrolled patients with indolent NHLs that had no response to, or had advanced on rituximab-containing regimens, the vast majority of subjects enrolled in this study had relapsed or refractory FL. There were very low numbers of patients with other indolent NHLs enrolled in the trial so the safety and efficacy of Gazyva (obinutuzumab) in other NHL populations could not be evaluated. [2 10]
- ***Use in DLBCL:*** A phase 3 study [GOYA] compared Gazyva (obinutuzumab) plus chemotherapy (G-CHOP regimen) with rituximab plus chemotherapy (R-CHOP) in patients with previously untreated DLBCL. There was no difference in PFS between the two groups. There was a higher incidence of grade 3 to 5 AEs in the G-CHOP arm. Additionally, there is no evidence demonstrating that Gazyva (Obinutuzumab) is superior to rituximab in the subsequent-line DBLCL treatment setting. [14]
- ***Use in FL with lenalidomide:*** There is no good evidence that Gazyva (obinutuzumab) plus lenalidomide is superior to other chemoimmunotherapy regimens used for the treatment of relapsed or refractory FL. Current studies are limited to small, single-arm trials that evaluate ORR as the primary endpoint. [15]

- Gazyva (obinutuzumab) has not been evaluated in non-cancer B-cell mediated conditions (e.g., rheumatoid arthritis).

Safety [2]

- Package labeling for Gazyva (obinutuzumab) carries a boxed warning for reactivation of hepatitis B virus and for progressive multifocal leukoencephalopathy (PML).
- Infusion reactions are common and may be severe or fatal. Premedication is recommended and the first infusion should be split over two days, with 100 mg infused on day 1 and 900 mg infused on day 2.
- Gazyva (obinutuzumab) should only be administered by a healthcare professional (HCP) with access to appropriate medical support (e.g., crash cart).
- Common adverse effects (incidence $\geq$ 10%) include: infusion reactions, neutropenia, thrombocytopenia, anemia, pyrexia, cough, and musculoskeletal disorders.
- Live virus vaccines should not be administered prior to or during therapy with Gazyva (obinutuzumab).

Dosing [2]

- Gazyva (obinutuzumab) should only be given intravenously through a dedicated line by a healthcare professional (HCP).
- A treatment course of Gazyva (obinutuzumab) is as follows (given in 28-day cycles) for CLL:
  - 100 mg IV on day of 1 cycle 1, then 900 mg IV on day 2 of cycle 1
  - 1,000 mg IV on days 8 and 15 of cycle 1
  - 1,000 mg IV on day 1 of cycles 2 through 6
- A treatment course of Gazyva (obinutuzumab) is as follows (given in 28-day cycles) for FL:
  - 1,000 mg IV on days 1, 8 and 15 of cycle 1
  - 1,000 mg IV on day 1 of cycles 2 through 6
  - Maintenance: 1,000 mg IV monotherapy every 2 months for up to 2 years
- The use of Gazyva (obinutuzumab) beyond one treatment course for CLL has not been studied.
- A single 1,000-mg dose of Gazyva (obinutuzumab) is indicated prior to initiating therapy with Columvi (glofitamab) to deplete circulating and lymphoid tissue B cells to reduce the incidence and severity of cytokine release syndrome (CRS).

Cross References
Bispecific T-cell engager (BiTE) Therapies for B-cell Lymphoma, Medication Policy Manual, Policy No. dru761
Products with Therapeutically Equivalent Biosimilars/Reference Products, Medication Policy Manual, Policy No. dru620
Venclexta, venetoclax, Medication Policy Manual, Policy No. dru462
PI3K Inhibitors, Medication Policy Manual, Policy No. dru706
Bruton's tyrosine kinase (BTK) inhibitors, Medication Policy Manual, Policy No. dru691

Codes	Number	Description
HCPCS	J9301	Injection, obinutuzumab (Gazyva), 10 mg

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Revision History

Revision Date	Revision Summary
3/6/2025	QL for follicular lymphoma corrected (no change to intent of coverage criteria).
9/19/2024	Added use in combination with Brukinsa (zanubrutinib) for relapsed/refractory follicular lymphoma as 'not medically necessary.'
3/21/2024	Removed archived Arzerra, ofatumumab (dru196) from Cross References. No change to intent of coverage criteria with this annual review.
9/14/2023	Added coverage for use as a one-time dose prior to initiation of Columvi (glofitamab) as indicated in the Columvi (glofitamab) package labeling.
3/16/2023	No criteria changes with this annual update.
3/18/2022	No criteria changes with this annual update.
7/16/2021	No criteria changes with this annual update.
10/28/2020	Added coverage criteria for use in combination with Calquence (acalabrutinib) for treatment-naïve CLL/SLL.
6/15/2020	Removed references to brand Rituxan from policy to account for upcoming changes in biosimilars policy (dru620).
4/22/2020	Added continuation of therapy (COT) criteria (no change to intent of coverage criteria).
10/23/2019	Effective 11/15/2019, added coverage criteria for use in previously-untreated CLL, in combination with Venclexta (venetoclax), a new FDA indication.
4/25/2019	No changes to coverage criteria with this annual update.
3/19/2019	Added use in untreated follicular lymphoma (first-line) as not medically necessary.
1/13/2017	Added coverage criteria for refractory or relapsing follicular lymphoma.
1/8/2016	Adjusted quantity limit to better reflect dosing in package labeling (limit to eight 1000-mg infusions as per package labeling).
1/7/2014	New policy.

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Medication Policy Manual

Policy No: dru351

Topic: Non-Preferred Intra-Articular Hyaluronic Acid Derivatives:

- Durolane (sodium hyaluronate)
- Euflexxa (1% sodium hyaluronate)
- Gel-One (sodium hyaluronate)
- Gelsyn-3 (sodium hyaluronate)
- GenVisc 850 (sodium hyaluronate)
- Hyalgan (sodium hyaluronate)
- Hymovis (high molecular weight hyaluronan)
- Monovisc (sodium hyaluronate)
- Supartz FX (sodium hyaluronate)
- Synojoynt (1% sodium hyaluronate)
- Triluron (1% sodium hyaluronate)
- Trivisc (sodium hyaluronate)
- Visco-3 (sodium hyaluronate)

Date of Origin: May 09, 2014

Committee Approval Date: December 7, 2023

Next Review Date: 2024

Effective Date: March 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Hyaluronic acid derivatives are injected directly into the knee joint to help improve the pain associated with osteoarthritis of the knee.

PLEASE NOTE: Preferred Intra-Articular Hyaluronic Acid (IAHA) products do not require pre-authorization. The preferred IAHA products are Synvisc, Synvisc-One, and Orthovisc.

Policy/Criteria

Most contracts require pre-authorization approval of non-preferred intra-articular hyaluronic acid derivatives prior to coverage.

I. Continuation of therapy (COT): Non-preferred intra-articular hyaluronic acid derivatives may be considered medically necessary for COT when full policy criteria below are met, including quantity limit.

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Non-preferred intra-articular hyaluronic acid derivatives may be considered medically necessary when criteria A and B are met.

A. Treatment with both of the following has been ineffective, contraindicated, or not tolerated:

1. Orthovisc (high molecular weight hyaluronan).

2. Synvisc or Synvisc-One (hylan G-F 20).

AND

B. The member has a documented diagnosis of osteoarthritis of the knee.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers intra-articular hyaluronic acid derivatives coverable only under the medical benefit (as provider-administered medications).

B. Initial authorization:

1. When pre-authorization is approved, intra-articular hyaluronic acid derivatives may be authorized in quantities of up to 2 treatment courses per knee for the initial 1-year period according to the chart below.

Product Name	**Number of Injections Per Treatment Course**
Durolane (sodium hyaluronate)	1 dose per knee
Euflexxa (1% sodium hyaluronate)	3 doses per knee
Gel-One (sodium hyaluronate)	1 dose per knee
Gelsyn-3 (sodium hyaluronate)	3 doses per knee
GenVisc 850 (sodium hyaluronate)	5 doses per knee
Hyalgan (sodium hyaluronate)	5 doses per knee
Hymovis (high molecular weight hyaluronan)	2 doses per knee
Monovisc (sodium hyaluronate)	1 dose per knee
Supartz FX (sodium hyaluronate)	5 doses per knee
Synojoynt (1% sodium hyaluronate)	3 doses per knee
Trivisc (sodium hyaluronate)	3 doses per knee
Visco-3 (sodium hyaluronate)	3 doses per knee
Triluron (1% sodium hyaluronate)	3 doses per knee

C. Continued authorization:

1. After the initial authorization, up to 2 courses per knee over a one-year period may be considered medically necessary if there is clinical documentation supporting clinical benefit from treatment, as defined by at least one of the following:

a. There is an improvement in pain or functional ability.

b. There has been a reduction in the use or frequency analgesics or anti-inflammatory medication.

2. Subsequent authorizations may be reviewed at least every 12 months to confirm that current medical necessity criteria are met, and that the medication is effective.

IV. Non-preferred intra-articular hyaluronic acid derivatives are considered not medically necessary for the following uses:

A. Osteoarthritis in joints other than the knee.

B. Skin wrinkles or other cosmetic indications.

V. Non-preferred intra-articular hyaluronic acids are considered investigational when used for all other conditions, including but not limited to:

A. Temporomandibular joint degenerative disorders.

B. Trigger finger.

Position Statement

- Hyaluronic acids are used as viscosupplementation and are injected directly into the knee joint to improve lubrication and reduce the pain associated with osteoarthritis of the knee.
- Given the inconclusive evidence for safety and efficacy, as well as inconsistent support from evidence-based clinical guidelines, the use of non-preferred hyaluronic acids is limited to patients with significant functional impairment that impacts quality of life or employment who have tried and failed conservative management strategies (analgesics and physical therapy/exercise) and/or intra-articular corticosteroid injections.
  * Standard therapies for treatment of knee pain related to arthritis include oral NSAIDs (such as ibuprofen, naproxen, or diclofenac), intra-articular corticosteroid injections, and physical therapy/exercises. These therapies are effective for providing pain relief for the vast majority of patients.
  * Hyaluronic acids are not recommended for routine use by the 2021 American Academy of Orthopedic Surgeons (AAOS) guidelines for management of osteoarthritis of the knee. The strength of this recommendation is characterized as “moderate” as it is based on multiple moderate-quality studies. [1 2]
  * 2019 American College of Rheumatology (ACR)/Arthritis Foundation (AF) guidelines conditionally recommend against the use of hyaluronic acids for osteoarthritis of the knee. The recommendation is based on lack of benefit in high-quality studies and the potential for harm associated with injections. The authors of a systematic review conducted as part of ACR/AF guideline development stated that benefit is restricted to low-quality studies and that in higher quality studies the benefit diminishes compared to saline injections alone. [3]

    * 2019 Guidelines by the Osteoarthritis Research Society International (OARSI) conditionally recommend the use of intra-articular hyaluronic acid when core treatments (exercise programs, dietary weight management, etc.) and pharmacologic therapies have been ineffective. [4]
    * 2020 Veteran's Administration (VA) guidelines suggest offering intra-articular hyaluronic acid derivatives for patients with persistent pain due to osteoarthritis of the knee inadequately relieved by other interventions. Although the recommendation is in favor of use, the guideline working group noted that the quality of evidence is low. [5]
- Several intra-articular hyaluronic acid products are available and there is little comparative evidence to differentiate the various products. Orthovisc, Synvisc, and Synvisc-One offer the best value for members.
- The use of intra-articular hyaluronic acids for osteoarthritis of the hip is considered not medically necessary. The majority of guidelines strongly or conditionally recommend against use in the hip due to high-quality evidence demonstrating a lack of benefit. [3,4] VA guidelines also noted the use of intra-articular hyaluronic acids in the hip have a higher risk profile due to proximity to the neurovascular structures. [5]
- There is inadequate evidence to support the use of hyaluronic acids in temporomandibular joint degenerative disorders or trigger finger.

CLINICAL EFFICACY

- Hyaluronic acids have not been proven in reliable clinical studies to be more effective than non-pharmacologic or generic analgesics such as acetaminophen and NSAIDs. The overall body of evidence is conflicting and additional high-quality studies are needed.
    * Systematic reviews of randomized controlled trials evaluating viscosupplementation in patients with osteoarthritis of the knee conclude that there are low-quality data available to determine efficacy and safety.
    * Clinical trials studying the effect of viscosupplementation on knee pain and functional outcomes have reported inconsistent results. Intra-articular injections are associated with a robust placebo-response; it is unclear if hyaluronic acid differs from placebo in a clinically meaningful way.
    * Several studies have reported no improvement in pain or mobility compared to placebo, simple analgesics, or exercise. [6-9]
    * Despite these limitations, authors of the Veteran's Administration (VA) guideline on knee osteoarthritis noted that large systemic reviews have shown some benefit and despite downgrades in the quality of evidence due to risk of bias, the outcomes were consistent across study groups. Thus, they have a weak recommendation in favor of offering hyaluronic acids as a treatment option. [5]
    * A 2015 Agency for Healthcare Research and Quality (AHRQ) review of clinical trials found no significant association between treatment with HLA and time to total knee arthroplasty (TKA). [10,11] The authors concluded that there is insufficient data to make any conclusions regarding the effect of HLA treatment on time to TKA.
- There is no reliable evidence, based on two comparative trials identified, to differentiate between hyaluronic acid products used for viscosupplementation in terms of safety or efficacy.

    * One randomized controlled trial in 660 patients with osteoarthritis of the knee did not demonstrate a difference in efficacy or safety of Synvisc compared with Orthovisc. [12]
    * A randomized trial comparing the effectiveness of Synvisc and Hyalgan is unreliable due to uncertain blinding which may have influenced patient reported outcomes. [13]

Guidelines

- The majority of guidelines offer conflicting recommendations with regard to intra-articular hyaluronic acids for the knee. Guidelines range from strong recommendations against use to conditional or weak recommendations in favor of use. Despite conflicting recommendations on hyaluronic acids, all guidelines recommend the use of conservative management strategies such as physical therapy, exercise, weight management, and NSAIDs.
- Systematic reviews have concluded that there is limited evidence to support subsequent treatment courses with hyaluronic acids; however, individual patients may benefit from additional courses of hyaluronic acids. [2,14] While there are conflicting recommendations among guidelines, the highest quality evidence supports minimal or no benefit.
- American College of Rheumatology (ACR)/Arthritis Foundation (AF) guidelines conditionally recommend against the use of hyaluronic acids for osteoarthritis of the knee. [3] The recommendation is based on a systematic review that concluded that the evidence supporting efficacy is limited to low-quality trials. When the analysis was limited to higher quality studies, the benefit of hyaluronic acid injections approached zero. Thus, the ACR/AF concluded that the best evidence does not demonstrate a benefit and there may be harms associated with the injections.
    * Conditional recommendations are used when the evidence is of low or very low-quality or the balances of risks and harms is close. Conditional recommendations meant to describe that the majority of informed patients would choose to follow the recommended course of action, but some would not.
    * ACR/AF Guidelines strongly recommend the use of intra-articular glucocorticoid injections for knee osteoarthritis and conditionally recommends them over other intra-articular injections (including hyaluronic acid). The recommendation is based on high-quality evidence for short-term efficacy. The guidelines do acknowledge that steroid injections may contribute to cartilage loss, but the clinical significance is unclear as change in cartilage thickness has not been shown to be associated with a worsening in pain, functioning, or other radiographic features. [3]
- The American Academy of Orthopedic Surgeons (AAOS) guidelines cannot recommend the routine use of hyaluronic acid for patients with symptomatic osteoarthritis of the knee. The use of hyaluronic acid was downgraded one level (from “strong” to “moderate”) due to a lack of generalized study results and moderate strength of supporting evidence. [1]
    * The AAOS position is based on assessment of the clinical meaningfulness of the result. The AAOS analysis concluded that the point estimate for the improvement in pain and function was less than half the pre-defined magnitude for clinically meaningful improvement.[1,2]

    * Statistically significant improvements were associated with high-molecular cross-linked hyaluronic acid but when compared to mid-range molecular weight, statistical significance was not maintained. This newer analysis did not demonstrate clinically relevant differences when compared to controls.[1]
    * Crosslinking features of the viscosupplementation products was assessed in two high quality studies. In patients with osteoarthritis, there was no difference between cross-linked and non-cross-linked HA.[1]
    * These guidelines also state that a specific subset of patients might benefit from intra-articular hyaluronic acids for the knee based on previous research reporting benefits in their use.[1]
- Osteoarthritis Research Society International (OARSI) guidelines conditionally recommend the use of hyaluronic acids after non-pharmacologic and NSAIDs/acetaminophen have been tried. The recommendations were also based on systematic reviews and meta-analyses of the available evidence though the guideline did account for differences in efficacy in high versus low-quality studies or address the impact of publication bias. [4]
- 2020 Veteran's Administration (VA) guidelines suggest offering intra-articular hyaluronic acid derivatives for patients with persistent pain due to osteoarthritis of the knee inadequately relieved by other interventions. Although the recommendation is in favor of use, the guideline working group noted that the quality of evidence is low. [5]

SAFETY

- The most common adverse events reported with hyaluronic acids include joint pain, stiffness and swelling, as well as injection site reactions. [15-22]

NOT MEDICALLY NECESSARY USES

- The use of intra-articular hyaluronic acids for osteoarthritis of the hip is considered not medically necessary.
    * 2019 ACR/AF Guidelines strongly recommend against the use of hyaluronic acid for the treatment of hip osteoarthritis due to high-quality evidence for lack of benefit. [3]
    * 2020 VA Guidelines conditionally recommend against the use of intra-articular hyaluronic acids in the hip due to high-quality evidence demonstrating a lack of benefit and safety concerns associated with the administration, specially the proximity to neurovascular structures. [5]

INVESTIGATIONAL USES

Use in Joints Other than the Knee

- Hyaluronic acids have been studied in the treatment of osteoarthritis of joints other than the knee, including the hip, shoulder, and ankle.
    * Small studies in patients with osteoarthritis of the ankle demonstrated that hyaluronic acid may be an effective treatment option; however, several larger, well-controlled trials have concluded that hyaluronic acid is not effective in this setting (no different than saline). [19-22]

* A randomized trial in patients with osteoarthritis of the shoulder did not demonstrate a significant difference in pain on movement between patients treated with sodium hyaluronate or placebo. [23]
* 2019 ACR/AF Guidelines strongly recommend against the use of hyaluronic acid for the treatment of hip osteoarthritis due to high-quality evidence for lack of benefit. [3]

Temporomandibular Joint (TMJ) degenerative disorders

- Several small studies have evaluated hyaluronic acids n in the treatment of symptoms of TMJ degenerative disorders (pain, range-of-motion, chewing efficiency). Larger, well-controlled studies are needed to confirm the benefit of hyaluronic acids and to determine the optimal frequency, dose, and product. [24-27]

Trigger finger

- One small randomized, controlled trial (N=36) evaluated patients with a diagnosis of trigger finder. Patients were randomized to hyaluronic acid or steroid injections, after the months of follow-up the percent of patients without triggering effect was numerically lower in the hyaluronic acid group, but not statistically significant. While promising the results must be confirmed in larger studies. Additionally, the optimal frequency, dose, and hyaluronic acid product has not been determined. [28]

Cross References
BlueCross BlueShield Association Medical Policy, 2.01.31 - Intra-articular Hyaluronan Injections for Osteoarthritis. [May 2021]

Codes	**Number**	**Description**
HCPCS	J7321	Hyaluronan or derivative, Hyalgan, Supartz FX, or Visco-3, for intra-articular injection, per dose
HCPCS	J7320	Hyaluronan or derivative, GenVisc 850, for intra-articular injection, per dose
HCPCS	J7322	Hyaluronan or derivative, Hymovis, for intra-articular injection, 1 mg
HCPCS	J7318	Hyaluronan or derivative, Durolane, for intra-articular injection, 1 mg
HCPCS	J7323	Hyaluronan or derivative, Euflexxa, for intra-articular injection, per dose
HCPCS	J7326	Hyaluronan or derivative, Gel-One, for intra-articular injection, per dose
HCPCS	J7327	Hyaluronan or derivative, Monovisc, for intra-articular injection, per dose
HCPCS	J7328	Hyaluronan or derivative, Gelsyn-3, for intra-articular injection, 0.1 mg
HCPCS	J7329	Hyaluronan or derivative, Trivisc, for intra-articular injection, 1 mg
HCPCS	J7332	Hyaluronan or derivative, Triluron, for intra-articular injection, 1 mg
HCPCS	J7331	Hyaluronan or derivative, Synojoynt, for intra-articular injection, 1 mg

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Revision History

Revision Date	Revision Summary
12/7/2023	No criteria changes with this annual review.
12/9/2022	No changes to criteria with this annual update.
9/23/2022	Updated preferred intra-articular hyaluronic acid (IAHA) products to Orthovisc, Synvisc, and Synvisc One. Added Synojoynt (1% sodium hyaluronate) to policy. Effective 1/1/2023.
7/16/2021	Effective 10/1/2021: • Preferred intra-articular hyaluronic acid (IAHA) products will not require pre-authorization. • Revised policy to allow coverage of non-preferred IAHA products in patients with osteoarthritis of the knee who have tried and failed all preferred IAHA products. • Products may be authorized for up to 1 year initially. Re-authorization requires documentation of ongoing clinical benefit.
4/22/2020	No criteria changes with this annual update. Policy position statements were updated to include updated guidelines from the American College of Rheumatology/Arthritis Foundation and Osteoarthritis Research Society International.
1/22/2020	• Added continuation of therapy (COT) criteria (no change to intent of coverage criteria). • Added sodium hyaluronate (Trivisc, Durolane, and Triluron) to policy.
1/31/2019	No criteria changes with this annual update.
12/14/2018	No criteria changes with this annual update.
12/8/2017	No criteria changes with this annual update. Added sodium hyaluronate (Durolane) to policy.
4/14/2017	No criteria changes with this annual update.
4/8/2016	Added temporomandibular joint disorders and trigger finger as investigational uses.
5/9/2014	New policy.

Drug names identified in this policy are the trademarks of their respective owners.

Medication Policy Manual | **Policy No:** dru355

Topic: Cyramza, ramucirumab | **Date of Origin:** July 11, 2014

Committee Approval Date: December 7, 2023 | **Next Review Date:** 2024

Effective Date: March 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Cyramza (ramucirumab) is an intravenously infused recombinant human monoclonal antibody that is used for the treatment of various cancers. It works by blocking the formation of blood vessels, thereby preventing the tumor from getting essential nutrients that it needs for growth.

Policy/Criteria

Most contracts require pre-authorization approval of Cyramza (ramucirumab) prior to coverage.

I. Continuation of therapy (COT): Cyramza (ramucirumab) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Cyramza (ramucirumab) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criterion A, B, C, or D below is met:

A. A diagnosis of **metastatic or unresectable, locally advanced gastric cancer** or **esophageal junction (GEJ) adenocarcinoma** when there was disease progression after prior treatment with fluoropyrimidine- or platinum-containing chemotherapy (see *Appendix 1*), or therapy with these regimens was not tolerated or is contraindicated.

OR

B. A diagnosis of squamous or non-squamous **metastatic non-small cell lung cancer (NSCLC)** when criteria 1 and 2 below are met:

1. There has been disease progression after one prior treatment with a platinum-containing regimen (see *Appendix 1*), unless either criterion a or b below is met:

a. If the NSCLC is ALK-positive, there has been progression of disease following treatment with an ALK inhibitor (see *Appendix 2*).

OR

b. If the NSCLC is positive for an epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 (L858R) substitution mutation, there has been progression of disease following treatment with an EGFR inhibitor (see *Appendix 2*) .

AND

2. Cyramza (ramucirumab) is given in combination with a taxane (see *Appendix 1*).

OR

C. A diagnosis of **metastatic colorectal cancer** when criteria 1 and 2 below are met:

1. There has been disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine (see *Appendix 3* for example regimens).

AND

2. Cyramza (ramucirumab) is given in combination with FOLFIRI (leucovorin, fluorouracil, and irinotecan).

OR

D. A diagnosis of **metastatic hepatocellular carcinoma (HCC)** when criteria 1 through 3 below are met:

1. A documented alpha fetoprotein of ≥ 400 ng/mL.

AND

2. There has been disease progression on, or intolerance to, at least one prior systemic HCC regimen (see *Appendix 5*).

AND

3. Cyramza (ramucirumab) will be used as a monotherapy.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Cyramza (ramucirumab) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Cyramza (ramucirumab) may be authorized as follows:

1. **Gastric cancer, esophageal junction (GEJ) adenocarcinoma, colorectal cancer (CRC), or hepatocellular carcinoma (HCC):** Up to 8 mg/kg every two weeks until disease progression.

2. **Non-small cell lung cancer (NSCLC):** Up to 10 mg/kg every 21 days until disease progression.

C. Authorization may be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

IV. Cyramza (ramucirumab) is considered not medically necessary for the first-line treatment of metastatic NSCLC with EGFR exon 19 deletions or exon 21 (L858R) mutations.

V. Cyramza (ramucirumab) is considered investigational when used for all other conditions, including but not limited to:

A. Brain cancer.
B. Breast cancer.
C. Prostate cancer.
D. Renal cell carcinoma (RCC).

VI. Cyramza (ramucirumab) is considered investigational when used concomitantly with any other targeted therapy, including, but not limited to bevacizumab, Erbitux (cetuximab), Gilotrif (afatinib), Iressa (gefitinib), Nexavar (sorafenib), Opdivo (nivolumab), Stivarga (regorafenib), Vectibix (panitumumab), Xalkori (crizotinib), Zaltrap (ziv-aflibercept), or Zykadia (ceritinib).

Position Statement

- Cyramza (ramucirumab), a human IgG1 monoclonal antibody that binds to vascular endothelial growth factor (VEGF) receptors.
- The intent of this policy is to cover Cyramza (ramucirumab) for the indications and dose for which it has been shown to be safe and effective, as detailed in the coverage criteria
- Cyramza (ramucirumab) is approved:
  * As a monotherapy or in combination with paclitaxel for the treatment of advanced gastric cancer or advanced gastro-esophageal junction (GEJ) adenocarcinoma after prior treatment with front-line fluoropyrimidine- or platinum-containing chemotherapy.
  * In combination with erlotinib, for first-line treatment of metastatic non-small cell lung cancer with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) mutations.
  * In combination with docetaxel for the treatment of metastatic non-small cell lung cancer (NSCLC) after prior treatment with front-line platinum-based chemotherapy (with or without maintenance therapy). Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Cyramza (ramucirumab).
  * For metastatic colorectal cancer when there has been disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine. Cyramza (ramucirumab) is given in combination with FOLFIRI. In the pivotal clinical trial in patients with locally advanced or metastatic gastric cancer or GEJ adenocarcinoma, a small but statistically significant improvement in overall survival (~ 5.5 weeks) was reported with Cyramza (ramucirumab) relative to best supportive care in the second-line, recurrent disease setting.

* For advanced hepatocellular carcinoma (HCC), as a single agent when there is an alpha-fetoprotein (AFP) level ≥ 400 ng/mL and disease progression on, or intolerance to, front-line Nexavar (sorafenib). It was approved in this setting based on a single, placebo-controlled trial.

- In the pivotal clinical trial for second-line NSCLC, a small but statistically significant improvement in overall survival (~5.6 weeks) was reported with Cyramza (ramucirumab) in combination with docetaxel relative to placebo after progression on front-line therapy.
- In the pivotal clinical trials for metastatic colorectal cancer, Cyramza (ramucirumab) plus FOLFIRI demonstrated a 1.6-month overall survival advantage compared to placebo plus FOLFIRI in patients who had disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine.
- Cyramza (ramucirumab) is considered not medically necessary for the first-line treatment of EGFR mutated NSCLC. In the pivotal trial in this setting, combination therapy with ramucirumab and erlotinib improved progression free survival by ~7 months. However, PFS is not a clinically relevant endpoint in metastatic NSCLC as it has not been found to accurately predict overall survival or quality of life. There is currently no evidence that the combination of Cyramza (ramucirumab) and erlotinib provides any clinically meaningful benefit over erlotinib alone, such as improved overall survival or quality of life. Furthermore, combination therapy adds toxicity compared to erlotinib alone. Rates of serious adverse events were higher in patients who received combination therapy. Cyramza (ramucirumab) in combination is covered in patients with NSCLC who progressed after treatment with platinum-based chemotherapy.
- A single placebo-controlled trial compared Cyramza (ramucirumab) with best supportive care (BSC) in elderly patients with advanced HCC with AFP levels ≥ 400 ng/ml who had disease progression on first-line Nexavar (sorafenib). The majority of subjects had cancer that had spread beyond the liver. Subjects on Cyramza (ramucirumab) had a one-month longer median survival than those receiving BSC.
- There is interest in studying Cyramza (ramucirumab) in other cancers, such as breast cancer, based on its pharmacology; however, there is currently no published, peer-reviewed evidence that supports clinical benefit in other cancers at this time.
- Cyramza (ramucirumab) may be covered for the doses studied and shown to be safe and effective (as detailed in the coverage criteria), until disease progression.
- The prescribing information for Cyramza (ramucirumab) includes a boxed warning describing an increased risk of hemorrhage, gastrointestinal perforation, and impaired wound healing. Death from hemorrhage has been reported.
- Common side effects include hypertension and diarrhea. Infusion reactions may also occur. Premedication with intravenous diphenhydramine is recommended. Dexamethasone and acetaminophen may be added for more severe infusion reactions.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy

Advanced Gastric Cancers

The body of evidence for advanced gastric cancers includes two randomized controlled trials (RCTs): one using Cyramza (ramucirumab) as a single agent and one using Cyramza (ramucirumab) in combination with chemotherapy.

- A published, randomized, double-blind, placebo-controlled trial (REGARD) evaluated the efficacy of Cyramza (ramucirumab) relative to placebo in patients with previously treated advanced gastric or gastro-esophageal junction (GEJ) adenocarcinoma. [1]
    * The study enrolled 355 patients who had failed prior therapy with a fluoropyrimidine- or platinum-containing chemotherapy regimen.
    * There was a modest improvement in overall survival in patients receiving Cyramza (ramucirumab) versus best supportive care (5.2 months and 3.8 months, respectively).
- An unpublished, randomized, double-blind, placebo-controlled trial (RAINBOW) evaluated the efficacy of Cyramza (ramucirumab) plus paclitaxel versus paclitaxel alone in patient with previously treated advanced gastric or GEJ adenocarcinoma. [2]
    * The study enrolled 665 patients who had failed prior therapy with a fluoropyrimidine- or platinum-containing chemotherapy regimen.
    * There was a modest improvement in overall survival in patients receiving Cyramza (ramucirumab) plus paclitaxel versus those receiving paclitaxel alone (9.6 months and 7.4 months, respectively).
- There is currently no evidence evaluating the efficacy of Cyramza (ramucirumab) in the first-line advanced gastric or GEJ adenocarcinoma setting.

- The National Comprehensive Cancer Network (NCCN) gastric cancer guideline lists Cyramza (ramucirumab) as a category 1 option for the second-line treatment of metastatic or locally advanced gastric cancer or GEJ adenocarcinoma when used as monotherapy or in combination with paclitaxel. [3]

EGFR Mutated Non-Small Cell Lung Cancer (NSCLC)

- A randomized, double-blind, placebo-controlled (RELAY study) evaluated the efficacy of Cyramza (ramucirumab) in combination with erlotinib versus erlotinib alone as first-line therapy in patients with stage IV NSCLC with EGFR exon 19 deletions or exon 21 (L858R) mutations. [4]
- Median investigator assessed PFS 19.4 months in the ramucirumab/erlotinib group compared to 12.4 months in the erlotinib group (HR 0.59, 95% CI 0.46 to 0.76).
- PFS is not a clinically relevant endpoint in metastatic NSCLC as it has not been found to accurately predict overall survival or quality of life.
- There is currently no evidence that the combination of Cyramza (ramucirumab) and erlotinib provides any clinically meaningful benefit over erlotinib alone, such as improved overall survival (OS) or quality of life. OS data from the pivotal front-line trial will be evaluated in the future after the data matures.
- The combination of Cyramza (ramucirumab) and erlotinib also added toxicity compared to erlotinib alone. Rates of adverse events, including diarrhea (75% versus 65%), hypertension (50% versus 40%), increased ALT (49% versus 35%), increased AST (49% versus 33%), stomatitis (46% versus 36%), decreased appetite (32% versus 19%), dysgeusia (23% versus 12%), and weight loss (19% versus 6%) were higher with combination therapy.

Non-Small Cell Lung Cancer (NSCLC)

- A published, randomized, double-blind, placebo-controlled trial (REVEL study) evaluated the efficacy of Cyramza (ramucirumab) plus docetaxel versus placebo plus docetaxel as second-line therapy in patients with stage IV NSCLC. [5]
    * The study enrolled 1,253 patients whose disease had progressed during or after first-line platinum-based chemotherapy with or without bevacizumab or maintenance therapy.
    * Patients whose only previous therapy for advanced or metastatic disease was EGFR tyrosine kinase inhibitor monotherapy were excluded from the study.
    * There was a modest improvement in overall survival in patients receiving Cyramza (ramucirumab) plus docetaxel versus those receiving docetaxel alone (10.5 months and 9.1 months, respectively).
- There is currently no evidence evaluating the efficacy of Cyramza (ramucirumab) beyond the second-line setting.
- The NCCN NSCLC guideline lists Cyramza (ramucirumab) in combination with docetaxel as a category 2A option for metastatic disease in the second-line setting. [3]

Metastatic Colorectal Cancer

- A published, randomized, double-blind, placebo-controlled trial (RAISE study) evaluated the efficacy of Cyramza (ramucirumab) versus placebo in combination with second-line FOLFIRI (leucovorin, fluorouracil, and irinotecan) for metastatic colorectal cancer in patients with disease progression during or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine. [6]

- The study included 1,072 patients who had disease progression during or within 6 months of the last dose of first-line therapy. The primary endpoint was overall survival (OS).
- Median OS was 13.3 months (95% CI 12.4 – 14.5) for Cyramza (ramucirumab)-treated patients compared to 11.7 months (95% CI 10.8 – 12.7) for placebo-treated patients. However, the clinical significance of a 1.6-month survival advantage in colorectal cancer is uncertain.
- The NCCN colon cancer and rectal cancer guidelines include Cyramza (ramucirumab) in combination with FOLFIRI as a category 2A recommendation for therapy after first progression. Bevacizumab plus FOLFIRI is the preferred option in this setting. [3]

Hepatocellular carcinoma (HCC)

- In a phase 3 study (REACH) in 565 patients with previously treated hepatocellular carcinoma, treatment with second-line Cyramza (ramucirumab) failed to improve overall survival over best supportive care. [7,8]
- However, a subsequent trial (REACH-2) limited to patients with elevated AFP levels found a small improvement in OS (one month). The placebo-controlled trial compared ramucirumab with best supportive care (BSC) in elderly patients with advanced HCC. [9]
    * All patients had AFP levels > 400 ng/ml and disease progression on first-line sorafenib.
    * The majority of subjects had cancer that had spread beyond the liver. The trial enrolled patients with Child-Pugh Class A disease, BCLC stage B and no longer amenable to locoregional therapy, or BCLC stage C.
    * Subjects on Cyramza (ramucirumab) had a small, one-month improvement in median survival than those receiving BSC (8.5 versus 7.3 months).
- Cyramza (ramucirumab) is a NCCN category 1 recommendation as a subsequent-line treatment option for advanced HCC when the AFP level is ≥ 400 ng/mL. [3]

Other Cancer Settings and Conditions

- There are ongoing clinical trials designed to evaluate the efficacy of Cyramza (ramucirumab) in brain cancer, prostate cancer, and renal cell carcinoma; however, there is currently no clinical evidence to support its use in these conditions. [10]
- In a phase 3 study in patients with human epidermal growth factor receptor 2 (HER2)-negative, unresectable, locally recurrent or metastatic breast cancer, the addition of Cyramza (ramucirumab) to docetaxel failed to improve overall survival over docetaxel alone. [11]
- A phase 2, Italian study compared Cyramza (ramucirumab) plus gemcitabine with gemcitabine alone as a second-line therapy in patients with advanced malignant pleural mesothelioma (MPM). [12] Though the authors concluded there was improved overall survival in the Cyramza (ramucirumab) treatment arm, the clinical relevance of the finding is not known as gemcitabine is not the standard of care for second-line treatment of MPM in the U.S. Of note, the subsequently updated NCCN guidelines do not include the use of Cyramza (ramucirumab) for advanced MPM.

Safety [13]

- The prescribing information for Cyramza (ramucirumab) includes a boxed warning describing an increased risk of hemorrhagic events, gastrointestinal perforation, and impaired wound healing with Cyramza (ramucirumab). Some cases of hemorrhage have resulted in death.
- The most common adverse events reported with Cyramza (ramucirumab) as a single agent include hypertension and diarrhea.
- The most common adverse reactions reported with Cyramza (ramucirumab) plus paclitaxel include fatigue, neutropenia, diarrhea, and epistaxis. When used in combination with docetaxel, the most common adverse reactions reported include neutropenia, fatigue/asthenia, and stomatitis/mucosal inflammation.
- The most common adverse reactions reported with Cyramza (ramucirumab) plus erlotinib include infections, hypertension, diarrhea, stomatitis, proteinuria, alopecia, epistaxis, peripheral edema, headache, and gastrointestinal hemorrhage. The majority of adverse events occurred at a greater frequency with combination therapy compared to erlotinib alone.
- Infusion-related reactions are also possible. Premedication with diphenhydramine is recommended. For more severe reactions, dexamethasone and acetaminophen may be used.
- Similar to other VEGF inhibitors, Cyramza (ramucirumab) may cause gastrointestinal perforation, impaired wound healing, and clinical deterioration in patients with cirrhosis.

Dosing considerations [13]

- The recommended dose of Cyramza (ramucirumab) for gastric cancer, esophageal junction adenocarcinoma, hepatocellular carcinoma, and metastatic colorectal cancer is 8 mg/kg intravenously every two weeks until disease progression or unacceptable toxicity.
- For NSCLC in combination with docetaxel, the recommended dose of Cyramza (ramucirumab) is 10 mg/kg intravenously on day 1 of a 21-day cycle prior to docetaxel infusion until disease progression or unacceptable toxicity.
- For EGFR mutated NSCLC in combination with erlotinib, the recommended dose of Cyramza (ramucirumab) is 10 mg/kg intravenously every two weeks, until disease progression or unacceptable toxicity.

Appendix 1: Platinum, Taxane and Fluoropyrimidine Medications

Platinum Medications	Fluoropyrimidine Medications	Taxane Medications
Cisplatin	Xeloda (capecitabine)	Jevtana (cabazitaxel)
Carboplatin	Floxuridine	Docetaxel
Eloxatin (oxaliplatin)	Fluorouracil (5-FU, Adrucil)	- Paclitaxel - Abraxane (nab-paclitaxel)

Appendix 2: EGFR and ALK Inhibitors Used in the Treatment of Metastatic Lung Cancer

EGFR Inhibitors	ALK Inhibitors
Gilotrif (afatinib)	Alecensa (alectinib)
Iressa (gefitinib)	Alunbrig (brigatinib)
Tagrisso (osimertinib)	Lorbrena (lorlatinib)
Tarceva (erlotinib)	Xalkori (crizotinib)
Vizimpro (dacomitinib)	Zykadia (ceritinib)

Appendix 3: Example Chemotherapy Regimens for Metastatic Colorectal Cancer Containing bevacizumab, oxaliplatin, and a fluoropyrimidine

Regimen Name	Included Medications
mFOLFOX6 + bevacizumab	Oxaliplatin, leucovorin, fluorouracil (5-FU), bevacizumab
CapeOx + bevacizumab	Oxaliplatin, capecitabine, bevacizumab
FOLFIRI + bevacizumab	Irinotecan, leucovorin, fluorouracil (5-FU), bevacizumab
FOLFOXIRI + bevacizumab	Irinotecan, oxaliplatin, leucovorin, fluorouracil (5-FU), bevacizumab

Appendix 4: Child-Pugh Classification Of Severity Of Liver Disease

Child-Pugh Classification	**Points**		
A: well-compensated disease	5 to 6		
B: significant functional compromise	7 to 9		
C: decompensated disease	10 to 15		
	Points Assigned		
Parameter	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL)	< 2	2 to 3	> 3
Albumin (g/dL)	> 3.5	2.8 to 3.5	< 2.8
Prothrombin Time			
Seconds over control	1 to 3	4 to 6	>6
INR	< 1.7	1.8 to 2.3	> 2.3
Encephalopathy	None	Grade 1 to 2	Grade 3 to 4

Appendix 5: First-line Regimens Used in the Treatment of Hepatocellular Carcinoma [3]

NCCN Front-Line HCC Regimens [category 1 recommendations]
Preferred regimens:
Tecentriq (atezolizumab) + bevacizumab for Child-Pugh Class A disease
Imjudo (tremelimumab) + Imfinzi (durvalumab)
Other recommended regimens:
Nexavar (sorafenib), for Child-Pugh Class A disease (category 2A for class B7)
Lenvima (lenvatinib), for Child-Pugh Class A disease
Imfinzi (Durvalumab)

Cross References
Molecular Analysis for Targeted Therapy of Non-Small Cell Lung Cancer (NSCLC), Medical Policy Manual, Genetic Testing Policy No. 56
Cabozantinib-containing medications, Medication Policy Manual, Policy No. dru290
Imfinzi, durvalumab, Medication Policy Manual, Policy No. dru500
Imjudo, tremelimumab, Medication Policy Manual, Policy No. dru737
Keytruda, pembrolizumab, Medication Policy Manual, Policy No. dru367
Lenvima, lenvatinib, Medication Policy Manual, Policy No. dru398
Nexavar, sorafenib, Medication Policy Manual, Policy No. dru134
Opdivo, nivolumab, Medication Policy Manual, Policy No. dru390
Stivarga, regorafenib, Medication Policy Manual, Policy No. dru284
Tecentriq, atezolizumab, Medication Policy Manual, Policy No. dru463
Zaltrap, ziv-aflibercept, Medication Policy Manual, Policy No. dru279

Codes	Number	Description
HCPCS	J9308	Injection, ramucirumab (Cyramza), 5 mg

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Revision History

Revision Date	Revision Summary
12/7/2023	No criteria changes with this annual review.
12/9/2022	• Updated in standard language in policy. • No changes to coverage criteria with this annual update.
1/20/2021	• COT language was updated (No change to intent of coverage criteria) • The list of acceptable prerequisite therapies under the HCC criteria (criterion II.D.2.) was expanded to include additional medication regimens because Nexavar (sorafenib) is no longer the only available front-line therapy recommended for use in this setting.
10/28/2020	Added first-line treatment of EGFR mutated NSCLC as not medically necessary.
6/15/2020	Removed references to brand Avastin from policy to account for upcoming changes in biosimilars policy (dru620).
1/22/2020	Added continuation of therapy (COT) criteria (no change to intent of coverage criteria).
7/24/2019	Add coverage criteria for advanced HCC, based on new evidence and indication (effective 8/15/2019).
1/31/2019	No changes to coverage criteria with this annual update.
6/15/2018	• Coverage criteria were updated to include <u>any</u> EGFR or ALK inhibitor as satisfying the condition for prior therapy in lung cancer to recognize the additional products now available to treat these mutations. • The authorization period was clarified to state that ramucirumab can be covered in the stated doses 'until disease progression'. This was always the intent of the policy, but is now explicitly stated.
9/8/2017	No changes to coverage criteria with this annual update.
9/9/2016	No changes to coverage criteria with this annual update
7/11/2014	New policy.

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Medication Policy Manual | **Policy No:** dru367

Topic: Keytruda, pembrolizumab | **Date of Origin:** November 13, 2014

Committee Approval Date: September 19, 2024 | **Next Review Date:** 2025

Effective Date: December 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Keytruda (pembrolizumab) is an intravenously infused immunotherapy that is used in the treatment of many different types of cancers.

Policy/Criteria

Most contracts require pre-authorization approval of Keytruda (pembrolizumab) prior to coverage.

I. Continuation of therapy (COT): Keytruda (pembrolizumab) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Keytruda (pembrolizumab) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) confirming that one of the following criterion A through R below are met:

A. A diagnosis of **Merkel cell carcinoma** (MCC), **unresectable locally advanced or metastatic**, when criteria 1, 2, and 3 below are met:

1. No prior systemic therapy (chemotherapy or immunotherapy) used in the advanced setting.

AND

2. Keytruda (pembrolizumab) will be used as monotherapy.

AND

3. No prior programmed death receptor-1 (PD-1) blocking antibody (PD-1 inhibitor) or programmed death-ligand 1 (PD-L1) blocking antibody therapy (see *Appendix 1*).

OR

B. A diagnosis of **cervical cancer** when criterion 1 or 2 below is met:

1. Diagnosis of **cervical cancer, recurrent or metastatic**, when criteria a through c below are met:

a. The tumor is PD-L1 positive as defined by a Combined Positive Score of 1 or more (CPS ≥ 1).

AND

b. Keytruda (pembrolizumab) will be used in one of the following two settings (i or ii):

i. As monotherapy when there has been disease progression on or after chemotherapy.

OR

ii. In combination with chemotherapy when used in patients who have had no prior systemic therapy for advanced disease.

AND

c. No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

OR

2. Diagnosis of **cervical cancer, unresectable locally advanced, International Federation of Gynecology and Obstetrics (FIGO) 2014 Stage III to IVA** when criteria a through d below are met:

a. One of the following histologies: squamous cell carcinoma (SCC), adenocarcinoma, or adenosquamous carcinoma.

AND

b. No prior definitive surgery, radiation, or systemic therapy in the advanced disease setting.

AND

c. Keytruda (pembrolizumab) will be used in combination with chemoradiation [e.g., a platinum plus external beam radiation therapy (EBRT)].

AND

d. No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

OR

C. A diagnosis of **gastric or gastroesophageal junction (GEJ) cancer** when criterion 1 or 2 below is met:

1. A diagnosis of **HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma, unresectable locally advanced or metastatic,** when criteria a through d below are met:

a. The tumor expresses PD-L1 as defined by a Combined Positive Score of 1 or more (CPS ≥1).

AND

b. No prior systemic therapy in the advanced disease setting.

AND

c. Keytruda (pembrolizumab) will be used in combination with trastuzumab plus fluoropyrimidine- (e.g., fluorouracil, capecitabine) and platinum-containing (e.g., cisplatin, oxaliplatin) chemotherapy.

AND

d. No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

OR

2. A diagnosis of **HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma, unresectable locally advanced or metastatic,** when criteria a through d below are met:

a. The tumor expresses PD-L1 as defined by a Combined Positive Score of 1 or more (CPS ≥1).

AND

b. No prior systemic therapy in the advanced disease setting.

AND

c. Keytruda (pembrolizumab) will be used in combination with fluoropyrimidine- (e.g., fluorouracil, capecitabine) and platinum-containing (e.g., cisplatin, oxaliplatin) chemotherapy.

AND

d. No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

OR

D. A diagnosis of **esophageal cancer** when criterion 1 or 2 below is met:

1. A diagnosis of **esophageal cancer, squamous cell carcinoma of the esophagus (ESCC)**, **recurrent unresectable locally advanced or metastatic,** when criteria a through d below are met:

a. Disease progression on or after prior systemic therapy.

AND

b. The tumor is PD-L1 positive as defined by a Combined Positive Score of 10 or more (CPS ≥ 10).

AND

c. Keytruda (pembrolizumab) will be used as monotherapy.

AND

d. No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

OR

2. A diagnosis of **esophageal (adenocarcinoma or ESCC) or gastroesophageal junction (GEJ) cancer, unresectable locally advanced or metastatic,** when criteria a through e below are met:

a. The patient is not a candidate for surgical resection or definitive chemoradiotherapy (CRT).

AND

b. The tumor is PD-L1 positive as defined by a Combined Positive Score of 10 or more (CPS $\geq$ 10).

AND

c. Keytruda (pembrolizumab) will be used in combination with platinum (e.g., cisplatin or oxaliplatin) and fluoropyrimidine (e.g., fluorouracil or capecitabine) based chemotherapy.

AND

d. No prior systemic therapy in the advanced disease setting.

AND

e. No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

OR

E. A diagnosis of **head and neck squamous cell cancer (HNSCC), recurrent or metastatic,** and no prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

OR

F. A diagnosis of **biliary tract cancer (BTC), unresectable locally advanced or metastatic,** when criteria 1 through 3 below are met:

1. No prior systemic therapy in the advanced disease setting.

AND

2. Keytruda (pembrolizumab) will be used in combination with gemcitabine and cisplatin.

AND

3. No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

OR

G. A diagnosis of **hepatocellular carcinoma (HCC)** when criteria 1 through 5 below are met:

1. The HCC is secondary to hepatitis B virus (HBV) infection.

AND

2. A documented Child-Pugh score of 5 or 6 (Class A).

AND

3. Disease progression on, or intolerance to at least one prior 'non-PD-1/PD-L1 inhibitor' systemic therapy for HCC (e.g., sorafenib or lenvatinib).

AND

4. Keytruda (pembrolizumab) will be used as monotherapy.

AND

5. No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

OR

H. A diagnosis of **melanoma** when criteria 1, 2, and 3 below are met**:**

1. Keytruda (pembrolizumab) will be used in one of the following settings (a or b):

a. **Unresected**: Unresectable locally advanced or metastatic melanoma (stage III or IV).

OR

b. **As adjuvant therapy (after surgery):** Stage IIB, IIC, or III melanoma after complete tumor resection.

AND

2. Keytruda (pembrolizumab) will be used as monotherapy.

AND

3. No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

OR

I. A diagnosis of **primary mediastinal B-cell lymphoma (PMBCL)** when criteria 1 through 3 below are met:

1. Disease progression on or after two or more lines of therapy [such as chemotherapy or hematopoietic stem cell transplant (HSCT); a.k.a. ASCT or bone marrow transplant (BMT)].

AND

2. Keytruda (pembrolizumab) will be used as monotherapy.

AND

3. No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

OR

J. A diagnosis of **non-small cell lung cancer (NSCLC),** when criterion 1, 2 or 3 below is met:

1. **Metastatic NSCLC (stage IV disease)**, when one of the following criteria below is met (a or b):

a. There is either no prior use of PD-1 inhibitors or PD-L1 inhibitors (see *Appendix 1*).

OR

b. Documented prior use of Keytruda (pembrolizumab) with NO progression of disease while on Keytruda (pembrolizumab) adjuvant therapy.

OR

2. **Earlier-stage, resected NSCLC, as adjuvant therapy only,** when all criteria (a through e) below are met.

a. Documented stage IB (T2a ≥4 cm), II, or IIIA disease

AND

b. Used in the adjuvant setting, after complete tumor resection.

AND

c. Used as a monotherapy.

AND

d. There is clinical documentation of previous adjuvant platinum-containing chemotherapy unless the patient is ineligible for any platinum-containing chemotherapy (such as cisplatin or carboplatin).

AND

e. There is no prior use of PD-1 inhibitors or PD-L1 inhibitors (see *Appendix 1*), including but not limited to use of Opdivo (nivolumab) in the neoadjuvant setting or Tecentriq (atezolizumab) in the adjuvant setting.

PLEASE NOTE: Platinum ineligibility may include poor kidney function, poor performance status (Eastern Cooperative Oncology Group [ECOG] score ≥2), heart failure, other comorbidities, etc.).

OR

3. **Earlier-stage, resectable NSCLC, as neoadjuvant therapy followed by adjuvant therapy**, when both criteria (a, b, and c) below are met:

a. Documented stage II, IIIA, or IIIB disease (tumors ≥4 cm and/or node positive)

AND

b. Keytruda (pembrolizumab) is used as follows (i and ii):

i. In combination with platinum-containing chemotherapy in the neoadjuvant setting (prior to surgical resection) for up to four cycles.

AND

ii. As monotherapy in the adjuvant setting (after surgical resection) for up to 13 cycles.

AND

c. No prior systemic anticancer therapy for NSCLC in any setting, including prior PD-1 inhibitors or PD-L1 inhibitors (see *Appendix 1*).

OR

K. A diagnosis of **classical Hodgkin Lymphoma (cHL), relapsed/refractory**, when criteria 1 and 2 below are met:

1. Disease progression on or after one or more lines of systemic therapy [such as chemotherapy or a hematopoietic stem cell transplant (HSCT, BMT)].

AND

2. No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

OR

L. A diagnosis of **urothelial carcinoma (UC, bladder cancer)**, when criteria 1 and 2 below are met:

1. Keytruda (pembrolizumab) will be used in one of the following settings (a, b, or c):

a. **First-line setting:** A diagnosis of **unresectable locally advanced (stage III) or metastatic (stage IV) bladder cancer,** when criteria i., ii., and iii. below are met:

i. The patient has not had prior systemic therapy (chemotherapy or immunotherapy) in the locally advanced or metastatic disease setting.

AND

ii. The patient is ineligible for any platinum-containing chemotherapy (such as cisplatin or carboplatin).

PLEASE NOTE: Any platinum ineligibility may include poor kidney function (CrCl<60), poor performance status (≥2), significant hearing loss (≥ 25 dB), grade 2-4 peripheral neuropathy, heart failure, other comorbidities, etc.

AND

iii. Keytruda (pembrolizumab) will be used either as a monotherapy or in combination with Padcev (enfortumab vedotin).

OR

b. **Subsequent-line setting:** A diagnosis of **unresectable locally advanced (stage III) or metastatic (stage IV) bladder cancer,** when criteria i. and ii. below are met:

i. There is clinical documentation of disease progression during or following platinum-containing chemotherapy,

AND

ii. Keytruda (pembrolizumab) will be used as monotherapy.

OR

c. A diagnosis of **non-muscle invasive bladder cancer (NMIBC)** when criteria i., ii., and iii. below are met:

i. The tumor is carcinoma in situ (CIS, stage Tis) OR recurrent Ta/T1 disease within 12 months of BCG therapy.

AND

ii. Prior use of Bacillus Calmette-Guerin (BCG) therapy documented.

AND

iii. Keytruda (pembrolizumab) will be used as monotherapy.

AND

2. No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

OR

M. A diagnosis of **colorectal cancer (CRC),** locally advanced or metastatic, when criteria 1 through 3 below are met:

1. The tumor is microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) CRC by immunohistochemistry (IHC) or polymerase chain reaction (PCR) testing.

AND

2. Keytruda (pembrolizumab) will be used as monotherapy.

AND

3. No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

OR

N. A diagnosis of **renal cell carcinoma (RCC)** when criteria 1 and 2 below are met:

1. Clear cell histology.

AND

2. Keytruda (pembrolizumab) will be used in one of the following settings (a or b):

a. A diagnosis of **recurrent or metastatic** disease when criteria i, ii, and iii are met:

i. No prior systemic therapy for advanced disease.

AND

ii. Use in combination with Inlyta (axitinib) or Lenvima (lenvatinib).

AND

iii. No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

OR

b. **As adjuvant therapy** (after surgery) when criteria i., ii., and iii. are met:

i. No prior systemic therapy for RCC.

AND

ii. Keytruda (pembrolizumab) will be administered as monotherapy.

AND

iii. Use in one of the following settings (1 or 2):

1. The tumor was **completely resected with clear margins** (the patient is tumor free based on MRI/CT scan) but there is intermediate-high or high-risk of RCC recurrence (per attestation or *Appendix 2*)

OR

2. The patient has RCC with stage M1 metastasis but there is **no evidence of disease (M1 NED) after nephrectomy and resection of metastatic lesions** (per attestation or *Appendix 2*).

OR

O. A diagnosis of **endometrial carcinoma, advanced (not curable with resection)**, when criteria 1 and 2 below are met:

1. Keytruda (pembrolizumab) will be used in one of the following two settings (a or b):

a. **Subsequent-line setting**: There has been disease progression on or after at least one prior systemic therapy.

OR

b. **First-line setting**: when criteria i and ii below are met:

i. As part of a front-line regimen (no prior systemic therapy).

AND

ii. Keytruda (pembrolizumab) is initiated in combination with carboplatin and paclitaxel.

AND

2. No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

OR

P. A diagnosis of **anal squamous cell carcinoma (aSCC), recurrent or metastatic,** when criteria 1, 2, and 3 below are met:

1. Disease progression on or after first-line cytotoxic chemotherapy.

AND

2. Keytruda (pembrolizumab) will be used as monotherapy.

AND

3. No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

OR

Q. A diagnosis of **cutaneous squamous cell carcinoma (cSCC),** when criteria 1, 2, and 3 below are met:

1. Documentation that the disease is metastatic or is not curable with surgical excision or radiation therapy.

AND

2. Keytruda (pembrolizumab) will be used as monotherapy.

AND

3. No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

OR

R. A diagnosis of **triple-negative breast cancer (TNBC)** when criteria 1 and 2 below are met:

1. Keytruda (pembrolizumab) will be used in one of the following settings (a or b):

a. **High-risk, early-stage (stage II or III) TNBC** in combination with cytotoxic chemotherapy as a neoadjuvant therapy, and then continued as a single agent as an adjuvant therapy after surgical excision.

OR

b. **Recurrent or metastatic TNBC** when criteria i through iii below are met:

i. The tumor is PD-L1 positive as defined by a Combined Positive Score of 10 or more (CPS $\geq$ 10).

AND

ii. No prior systemic therapy in the advanced disease setting.

AND

iii. Keytruda (pembrolizumab) will be given in combination with cytotoxic chemotherapy.

AND

2. No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

III. Administration, Quantity Limitations (QL), and Authorization Period

A. Regence Pharmacy Services considers Keytruda (pembrolizumab) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Keytruda (pembrolizumab) will be authorized as follows in *Table 1* below:

Table 1: QL and Authorization Period

Diagnosis	Dose [a]	Authorization Period(s) [b]	Total Coverable Doses and/or Duration of Therapy [b]
Earlier stage disease (resected or planned resection)			
➢ Neoadjuvant followed by adjuvant			
Neoadjuvant/adjuvant TNBC, early-stage	Up to 200 mg every 3 weeks [a]	Neoadjuvant -up to 8 doses (24 weeks) Adjuvant -up to 9 doses (27 weeks)	Until disease progression, total of 8 doses neoadjuvant followed by up to 9 doses adjuvant (51 weeks)
Neoadjuvant/adjuvant NSCLC, earlier-stage	Up to 200 mg every 3 weeks [a]	Neoadjuvant -up to four doses pre-surgical resection (12 weeks) Initial Adjuvant -up to 8 doses (24 weeks) Continued Adjuvant -up to 5 doses (15 weeks)	Until disease progression, total of 4 doses neoadjuvant followed by up to 13 doses adjuvant
➢ Adjuvant only			
Adjuvant ONLY: - NSCLC, earlier-stage - Melanoma - RCC	Up to 200 mg every 3 weeks [a]	Initial Adjuvant -up to 8 doses (24 weeks) [c] Continued Adjuvant -up to 10 doses (30 weeks) [c]	Until disease progression, up to 18 doses (54 weeks) [c]
Advanced disease (non-resectable)			
Melanoma, unresectable or metastatic	Up to 200 mg every 3 weeks [a]	Initial / Continued -up to 8 doses (24 weeks)	Until disease progression
All other covered diagnoses [d]	Up to 200 mg every 3 weeks [a]	Initial / Continued -up to 8 doses (24 weeks)	Until disease progression, up to 24 months

NSCLC: non-small cell lung cancer; RCC: renal cell carcinoma; TNBC: triple-negative breast cancer

[a] Alternative dosing regimen: up to 400 mg every 6 weeks

[b] All dose quantity limits are based on dosing every 3 weeks. Every 6-week dosing is coverable for half the number of doses (rounded to a whole number).

[c] Adjuvant therapy of '12 months' is limited to up to 17-18 doses (every 3 weeks) or 9 doses (every 6 weeks). See '*Dosing'* for additional information.

[d] Including advanced forms of diagnoses in the coverage criteria, except as specifically noted above in this table.

C. Reauthorization: Authorization **shall** be reviewed at least every 24 weeks for documented benefit. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met. Specifically, documentation that the medication is providing clinical benefit, including disease stability or improvement, and lack of disease progression, based on an assessment of change in tumor burden. If there is documentation of potential disease progression, a shortened authorization (up to three months) may be approved to allow time for clarification of response to Keytruda (pembrolizumab), including clinical re-evaluation of the patient and reimaging.

PLEASE NOTE: Additional doses of Keytruda (pembrolizumab) will not be authorized without a documented recent assessment by the treating provider (such as oncologist) with objective evidence of response to therapy, such as by re-imaging and use of iRECIST criteria.

D. For treatment beyond the maximum doses/duration of therapy specified above (in "QL and Authorization Period" Table 1): Authorization **shall** be reviewed at least every 24 weeks for documented benefit. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met. Specifically, documentation that the medication is providing clinical benefit, including disease stability or improvement, and lack of disease progression based on an assessment of change in tumor burden (as detailed above).

IV. Keytruda (pembrolizumab) is considered investigational when used for all other conditions, including but not limited to:

A. Triple negative breast cancer (TNBC) [except as specified in the sections above].

B. Microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) tumors [unless specified in the sections above].

C. Multiple myeloma.

D. Ovarian cancer.

E. Small cell lung cancer (SCLC).

F. Soft tissue sarcomas (STS), including uterine leiomyosarcoma (LMS).

G. TMB-H tumors (solid tumors with high mutational burden).

Position Statement

Summary

- Keytruda (pembrolizumab) is a human programmed death receptor-1 (PD-1) blocking monoclonal antibody (immunotherapy) used in the treatment of several types of cancers.
- The intent of this policy is to cover Keytruda (pembrolizumab) in settings where it has been shown to be safe and effective, as detailed in the coverage criteria, with consideration for other available treatment options.

    * Where there is lack of proven additional benefit and/or lack of demonstrated health outcome (such as overall survival or improved quality of life) relative to alternative therapies, use of Keytruda (pembrolizumab) alone or in combination with other therapies is not coverable ("not medically necessary" or "investigational").
    * It is important to note that the fact that a medication is FDA approved for a specific indication does not, in itself, make the treatment medically reasonable and necessary.

- Keytruda (pembrolizumab) is also FDA approved for use in the following conditions; however, the health plan considers these uses to be "investigational" (not covered) as Keytruda (pembrolizumab) has not demonstrated to provide any health benefit, based on the currently available evidence:
    * Adjuvant therapy for Stage IIB and IIC (completely resectable) melanoma.
    * MSI-H Tumors, other than CRC and endometrial carcinoma *(as described in the Clinical Efficacy section below).*
    * Tumor Mutational Burden-High (TMB-H) Solid Tumors (any).
- Many of the clinical indications for immunotherapies (PD-1, PD-L1, and others) have been approved by the FDA and endorsed by clinical guidelines based on surrogate measures such as overall tumor response rate (ORR) and progression-free survival (PFS) which are not proven to accurately predict clinically important outcomes such as improved overall survival or improved quality of life.
- *PD-L1 expression testing*: is required for coverage of many clinical indications for PD-1 and PD-L1 inhibitors.
    * There are several ways in which PD-L1 expression can be defined. In addition, how PD-L1 expression is defined varies by tumor type and setting.
    * PD-L1 expression is determined by the FDA-approved companion diagnostic testing, based on both the specific PD-1/PD-L1 inhibitor and the tumor type.
    * However, PD-L1 test results are not interchangeable across PD-1/PD-L1 inhibitors and/or indications. There is no conversion available from one type of test to another, such as combined positive score (CPS) versus tumor proportion score (TPS) versus percent of tumor cells (TC). Therefore, the correct test must be conducted for proper selection of patient populations for a given use.
- National Comprehensive Cancer Network (NCCN) guidelines recommend Keytruda (pembrolizumab) as a potential option in each of the treatment settings listed in the coverage criteria. In general, NCCN recommendations parallel the FDA approved indications.
- The PD-1 and PD-L1 inhibitors have the potential to cause immune-mediated adverse reactions that can result in pneumonitis, colitis, hepatitis, endocrinopathies, and nephritis.
- Keytruda (pembrolizumab) is coverable for up to the dose and quantity as specified in the coverage criteria.
    * It is administered until disease progression or unacceptable toxicity when used in melanoma (unresectable) and for up to 12 months as adjuvant therapy for resectable melanoma, resectable RCC, or resectable early-stage NSCLC.

    * For neoadjuvant/adjuvant therapy for very specific resectable cancers, a pre-specified number of doses (per the clinical trials) are administered as neoadjuvant therapy before surgery and, specific number of doses of adjuvant therapy after surgery (or until disease recurrence or unacceptable toxicity).
        - For high-risk, early-stage triple-negative breast cancer (TNBC), it is administered as neoadjuvant therapy for up to 24 weeks and adjuvant therapy for up to 27 weeks (or until disease recurrence or unacceptable toxicity).
        - For earlier stage NSCLC: it is administered as neoadjuvant therapy for up to 12 weeks and adjuvant therapy for up to 39 weeks (or until disease recurrence or unacceptable toxicity).
    * For its other advanced, non-resectable indications, it is given until disease progression, unacceptable toxicity, or for up to 24 months in patient without disease progression. Given that trials for most indications were specifically designed for a 24-month course of therapy, there is no conclusive additional benefit with higher doses or when given for longer durations.
- Optimal sequencing of chemotherapy and immunotherapy in many cancers is unknown or the data is evolving. At this time, sequential use of immunotherapies is not supported by current evidence. Specifically, there is no evidence to support the sequential use of different PD-1 or PD-L1 inhibitors once there is disease progression on prior PD-1 or PD-L1 inhibitor therapy, as well as use of adjuvant PD-1/PD-L1 inhibitor after neoadjuvant PD-1/PD-L1 inhibitor therapy (unless explicitly listed in the coverage criteria). Therefore, the use of sequential courses of PD-1/PD-L1 immunotherapy is not coverable.
- There are ongoing studies using Keytruda (pembrolizumab) in a variety of other cancers. However, although initial evidence may be promising, the potential for clinical benefit in these conditions is still being investigated.
- The use of Keytruda (pembrolizumab) for small cell lung cancer (SCLC) is considered investigational. The FDA indication for SCLC was withdrawn after confirmatory trials failed to demonstrate an improvement in any health outcome when used in this setting.
- *Reauthorization Criteria*: When coverage criteria are met, Keytruda (pembrolizumab) is authorized for six months (24 weeks) of therapy, after which time documentation must be provided to establish that the medication is effective. Specifically, there must be documentation of clinical benefit, including disease stability or improvement and there is a lack of disease progression, based on an assessment of change in tumor burden.
    * The standard of care for evaluation of response to cancer immunotherapy, such as Keytruda (pembrolizumab), is use of the iRECIST criteria for assessment of tumor burden. [1]
    * The iRECIST criteria include use of quantitative and qualitative criteria for assessment of change in tumor burden for target lesions and non-target lesions. [2]
        - Quantitative measurements for target lesions (tumor size and % change)
        - Qualitative evaluation for non-target lesions (present/disappeared/ unequivocal progression)

* Documentation of benefit must include an assessment of the most recent imaging ("restaging scans") by the treating oncologist. Given the complexity of the evaluation, including use of the iRECIST criteria, Keytruda (pembrolizumab) will not be reauthorized without an assessment of response to therapy, such a partial response (iPR), complete response (iCR), or stable disease (iSD).
* Use of immunotherapy may result in pseudoprogression, due to immune and T-cell activation, which can appear similar to tumor flare. If there is documentation of potential disease progression ["unconfirmed progressive disease (iUPD)"], a shortened authorization (up to three months) may be approved to allow time for clarification of response to Keytruda (pembrolizumab), including clinical re-evaluation of the patient and reimaging. Guidelines recommend reimaging for iUPD after 4-8 weeks.
* If a patient has confirmed, unequivocal new lesions (progression of disease, iPD), additional Keytruda (pembrolizumab) is not coverable. If a new lesion is equivocal, iUPD reassessment by the treating oncologist with repeat imaging would apply (as noted above).

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy

CERVICAL CANCER

Recurrent or metastatic

- Keytruda (pembrolizumab) received FDA Accelerated approval for use in recurrent or metastatic cervical cancer when tumors express PD-L1 (CPS $\geq$ 1) based on tumor response rates from a single-arm, open-label study [KEYNOTE-158]. To date, there is no evidence that it improves any clinically relevant outcome [e.g., improved overall survival (OS), symptom control, function, or quality of life (QOL)] in this disease setting. [3]
    * The current available evidence is limited to two small, uncontrolled, open-label Phase 1b/2 studies evaluated subjects with metastatic cervical cancer who had between one and four prior systemic therapies. Nearly all tumors expressed PD-L1 with a Combined Positive Score (CPS) of at least 1%. [4-6]
    * The reported objective response rate (ORR) in the pivotal study was 14.6%. Three patients (3.6%) had a complete response.
    * ORR has not been shown to accurately predict improvement in clinical endpoints in cervical cancer.
- A phase 3, double-blind RCT [KEYNOTE-826] evaluated the addition of Keytruda (pembrolizumab) to a platinum-based chemotherapy regimen in patients with carcinoma of the cervix that had not been treated with prior systemic chemotherapy and which was not amenable to curative treatment. [7]
    * Patients had persistent, recurrent, or metastatic adenocarcinoma, adenosquamous carcinoma, or squamous cell carcinoma of the cervix. Patients were naïve to prior systemic chemotherapy and PD-1/PD-L1 inhibitor therapy.
    * Patients were enrolled without regard to PD-L1 status; however, all patients were tested after enrolling in the study. Eighty-nine percent of patients in the study had a PD-L1 combined positive score (CPS) of at least 1.
    * Patients received either Keytruda (pembrolizumab) or placebo plus a platinum and paclitaxel (with or without bevacizumab). Chemotherapy was given for up to six cycles and Keytruda (pembrolizumab) was given for up to 35 cycles.
    * OS was significantly longer in the Keytruda (pembrolizumab) versus the placebo arm among patients with a PD-L1 CPS $\geq$ 1 (primary analysis population). The HR for death was 0.64 [95% CI: 0.50 to 0.81] with $p < 0.001$. There was also a statistically significant survival benefit in the entire population, which included patients with PD-L1 CPS < 1 ("All comers"). However, patients with a PD-L1 CPS $\geq$ 1 made up the vast majority (~90%) of the study population which likely confounded the "All comers" analysis by enriching the population with potential responders. A sub analysis in patients with PD-L1 CPS < 1 showed no survival benefit which supports this conclusion.

High-risk, locally advanced (FIGO 2014 Stage III/IVA)

- Keytruda (pembrolizumab) was also evaluated as an add-on therapy to chemoradiation for high-risk, locally advanced cervical cancer in a large placebo-controlled RCT [KEYNOTE A-18]. The current indication in this population is based on a subgroup from this study

that had International Federation of Gynecology and Obstetrics (FIGO) 2014 stage III to IVA disease (tumor involvement in the lower vagina with or without extension into the pelvic sidewall, or hydronephrosis/non-functioning kidney, or spread to adjacent pelvic organs). Patients with FIGO stage IVB disease were excluded from the study. [8]

* The study enrolled patients with the following disease histologies: Squamous cell carcinoma (SCC), adenocarcinoma, or adenosquamous carcinoma of the cervix.
* Patients enrolled in the study had no prior definitive surgery, radiation, or systemic therapy.
* The study compared Keytruda (pembrolizumab) 200 mg IV Q3W for 5 cycles plus cisplatin (5 to 6 cycles) and radiotherapy, followed by Keytruda (pembrolizumab) 400 mg IV Q6W as monotherapy for an additional 15 cycles with matching placebo plus chemoradiotherapy as described above.
* Ninety-three percent of the tumors had PD-L1 CPS $\geq$1.
* The median PFS was not reached in either treatment arm. The hazard ratio for progression or death was 0.59 [95% CI: 0.43, 0.82] in favor of Keytruda (pembrolizumab). The impact of this therapy on clinically relevant outcomes is unknown as the OS data is not mature.

- The NCCN cervical cancer guideline recommends the following: [9]
  * ***Recurrent or metastatic disease:*** Front-line platinum-based chemotherapy with or without bevacizumab. Keytruda (pembrolizumab) can be added for PD-L1-expressing tumors (CPS $\geq$ 1%).
  * ***FIGO 2014 stage III to IVA disease:*** Cisplatin or carboplatin plus external beam radiation therapy (EBRT) plus Keytruda (pembrolizumab).

COLORECTAL CARCINOMA (CRC), MSI-H or dMMR

- Keytruda (pembrolizumab) was initially approved for CRC as a subsequent therapy for locally advanced or metastatic MSI-H/dMMR CRC, when there is progression of disease on or after standard front-line therapy with fluoropyrimidine, oxaliplatin, and irinotecan, based on a combined cohort of 90 patients from several single-arm studies (a "basket" trial). [8,10]
  * The accelerated approval of Keytruda (pembrolizumab) was for microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumors was based on preliminary tumor response [overall response rate (ORR)] and duration of response (DOR) data from a "basket trial" pooled analysis of 149 patients across five different early phase, open-label trials (90 patients with CRC and 59 non-CRC patients).
  * Subjects enrolled in the basket trial had advanced solid tumors and at least one prior chemotherapy regimen. CRC-specific trials required prior CRC therapy.
  * In 90 CRC patients, tumor response rate was 36%. However, no other outcomes were measured, and clinical benefit has not been established.
  * Despite the low level of evidence, Keytruda (pembrolizumab) may be a reasonable treatment alternative in patients with in MSI-H/dMMR CRC when there is progressive disease on or after standard CRC therapies.

- Subsequently, the FDA approved Keytruda (pembrolizumab) for use as an initial therapy for MSI-H/dMMR CRC, based on an improvement in PFS in a single unblinded Phase 3 trial [KEYNOTE-177]. [10] Keytruda (pembrolizumab) was superior to investigator's choice of chemotherapy (fluorouracil-based chemotherapy with or without bevacizumab or cetuximab) for PFS. However, overall survival data, a secondary endpoint, was not mature at the time of FDA approval. Therefore, the clinical benefit is unknown. Of note, high crossover to Keytruda (pembrolizumab) will confound interpretation of future OS results.
- The NCCN CRC guideline recommends against the use of Keytruda (pembrolizumab) for MSI-H CRC in the adjuvant setting, meaning after surgery, but before any progression of disease. Standard therapies with fluoropyrimidine (fluorouracil, capecitabine), oxaliplatin, and irinotecan are recommended (with regimens such as FOLFOX, CAPEOX, or FOLFIRI). In the locally advanced and metastatic setting, treatment is recommended based on tumor markers, including KRAS wild type [Erbitux (cetuximab)], or prior therapies and may include addition of a VGEF inhibitor (bevacizumab). [9]

HEAD AND NECK SQUAMOUS CELL CANCER (HNSCC)

- Keytruda (pembrolizumab) was FDA approved as a <u>first-line</u> treatment for unresectable or metastatic HNSCC as a monotherapy OR in combination with standard chemotherapy, based on small improvement in overall survival (OS) in an open-label phase 3 trial [KEYNOTE-048]: [11]
    * The combination of Keytruda (pembrolizumab) and a platin plus fluorouracil improved median OS relative to Erbitux (cetuximab) plus a platin and fluorouracil (13.0 months versus 10.7 months, respectively; p = 0.0067).
    * A small survival advantage (statistically significant) was noted with use of Keytruda (pembrolizumab) <u>monotherapy</u> relative to Erbitux (cetuximab) plus a platin and fluorouracil in PD-L1-positive tumors (CPS $\geq$ 1). Median OS was 12.3 months and 10.3 months in the Keytruda (pembrolizumab) and chemotherapy arms, respectively. The advantage did not extend to the overall population (OS superiority was only for tumors with CPS $\geq$ 1).
- Keytruda (pembrolizumab) also has approval (Accelerated) as a <u>subsequent-line</u> therapy for recurrent or metastatic HNSCC as a single agent when used after progression of disease on or after a platinum-containing chemotherapy. Efficacy was based on improved tumor response rates in two uncontrolled, open-label studies, with a 16% objective response rate (ORR). A small proportion of complete responses (4.6%) was reported in one of the trials. The remainder were partial responses. To date, there is no evidence that it improves any clinically relevant outcome (e.g., improved survival, symptom control, function, or quality of life) in this setting. [8,12]
- There is no evidence to support the use of Keytruda (pembrolizumab) as a second-line therapy in patients unable to use first-line platinum-based chemotherapy for HNSCC.
- The NCCN head and neck cancers guideline lists use of Keytruda (pembrolizumab) for recurrent, unresectable, or metastatic HNSCC when used in the front-line treatment setting, as well as when used in the subsequent-line treatment setting. [9]

HEPATOCELLULAR CARCINOMA (HCC)

- Keytruda (pembrolizumab) received Accelerated FDA approval for use in HCC after progression of disease on, or intolerance to, first-line Nexavar (sorafenib) based on a small, single-arm, open-label Phase 2 preliminary study [KEYNOTE-224] in patients with Child-Pugh (CP) Class A disease that evaluated tumor response rate. Clinical benefit in this setting has not been demonstrated. [13] The confirmatory phase 3 trial [KEYNOTE-240] failed to demonstrate PFS or OS benefit. A subsequent phase 3 trial [KEYNOTE-394] demonstrated a very small improvement in OS in a more limited population and the FDA narrowed the approved indication to relapsed/refractory HCC due to hepatitis B virus (HBV), in CP-Class A only.
    * Subjects enrolled in the trial had progressive disease while on Nexavar (sorafenib) or had intolerable adverse effects to Nexavar (sorafenib) therapy.
    * Nearly all of the patients were Child-Pugh Class A (score of A5 or A6); however, a small portion (6%) had a score of B7/B8 (Class B).
    * Most patients (64%) had disease that had spread beyond the liver.
    * An ORR of 17% was reported in the trial. ORR has not been shown to accurately predict clinically relevant outcomes. Additionally, it is not known how Keytruda (pembrolizumab) compares with other second-line HCC therapies.
- The confirmatory phase 3 RCT [KEYNOTE-240] evaluating Keytruda (pembrolizumab) relative to placebo (best supportive care) in the second-line advanced HCC setting failed to meet the primary endpoints of PFS and OS. [14] There is the potential for this indication to be withdrawn in the future based on FDA guidance for Accelerated approvals that states: "Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials".
- A subsequent RCT [KEYNOTE-394] intended as the confirmatory trial for Keytruda (pembrolizumab) in relapsed or refractory unresectable or metastatic HCC demonstrated a <1-month improvement in median OS relative to placebo. The trial evaluated Asian patients (primarily conducted in China) who had HCC secondary to hepatitis B virus (HBV) infection. All patients had Child-Pugh Class A disease, and all had prior systemic therapy for HCC, the majority (83%) with sorafenib. The FDA subsequently updated the Keytruda (pembrolizumab) HCC indication to reflect the population used in this study (more narrow than initially approved). [15]
- The NCCN hepatocellular carcinoma guideline lists several recommended (category 1 and 2A) therapies for subsequent therapy for HCC, including Opdivo (nivolumab) alone or in combination with Yervoy (ipilimumab). Keytruda (pembrolizumab) is listed as an option for patients with Child-Pugh Class A disease who have not had prior checkpoint inhibitor therapy. [9]

BILIARY TRACT CANCER (BTC)

- An RCT [KEYNOTE-966] evaluated Keytruda (pembrolizumab) in patients with unresectable locally advanced or metastatic biliary tract cancer (BTC) as an add-on to front-line chemotherapy. [16]
    * Patients had histologically confirmed extra- or intrahepatic cholangiocarcinoma

(CCA) or gall bladder cancer and had not received prior therapy for their advanced disease. Patients treated with neoadjuvant or adjuvant therapy for resectable, non-metastatic disease were allowed to enroll if their disease recurred at least 6 months after completing these therapies.

  * The study compared Keytruda (pembrolizumab) plus gemcitabine/cisplatin with placebo plus gemcitabine/cisplatin (chemotherapy alone). Cisplatin was given for up to eight cycles, and Keytruda (pembrolizumab) was given for up to 35 cycles.
  * Sixty-eight percent of the tumors had PD-L1 CPS $\geq$1, though PD-L1 status was not a condition for enrollment.
  * The median OS was 12.7 months and 10.9 months in the Keytruda (pembrolizumab) and placebo treatment arms, respectively.

- Imfinzi (durvalumab) is also approved in this treatment setting with similar evidence and outcomes; however, there is no evidence directly comparing the two therapies.
- The NCCN BTC guideline list gemcitabine/cisplatin plus either Imfinzi (durvalumab) or Keytruda (pembrolizumab) among preferred, category 1 recommendations for the front-line treatment of unresectable or metastatic BTC. [9]

CLASSICAL HODGKIN LYMPHOMA (cHL)

- Keytruda (pembrolizumab) was FDA-approved in classical Hodgkin lymphoma based on a single-arm trial that evaluated tumor response rates in patients with relapsed or refractory disease. Patients in the study were heavily treatment-experienced. [8,17] To date, there is no evidence that Keytruda (pembrolizumab) improves any clinical outcome in this population.
  * Subjects enrolled in the trial had received a median of four prior therapies, including prior autologous hematopoietic stem cell transplant (61%) and/or Adcetris (brentuximab vedotin) 83%.
  * The ORR reported in the study was 69%, with 22% complete responses.
- Subsequently, the Keytruda (pembrolizumab) was studied in an open-label (not blinded) phase 3 RCT in an earlier line of therapy for relapsed or refractory cHL, after chemotherapy and/or hematopoietic stem cell transplant (HSCT), or in patients ineligible for HSCT in one unblinded Phase 3 trial [KEYNOTE-204]. [8]
  * Keytruda (pembrolizumab) was superior to brentuximab vedotin (BV, Adcetris), based on an improvement in PFS (13.2 months with pembrolizumab vs. 8.3 months with BV).
  * Overall survival data, a co-primary endpoint, was not mature at the time of the interim data analysis and the FDA approval. Therefore, the clinical benefit is unknown. Of note, a significant number of subjects received subsequent SCT (30% and 21% in the pembrolizumab and BV arms, respectively), which will confound future OS results.
- A small (N=38), single-arm, phase 2 study evaluated pembrolizumab plus gemcitabine/vinorelbine/liposomal doxorubicin (GVD) given for two to four cycles prior to autologous stem cell transplant as a second-line therapy for patients with relapsed/refractory cHL. [34170745]

    * Ninety-five percent of patients achieved a complete remission and 36 of 38 patients went on to receive an ASCT.
    * It is unknown how pembrolizumab + GVD compares with other regimens used in this setting, or if it improves long-term outcomes such as overall survival.
- The NCCN Hodgkin lymphoma guideline lists Keytruda (pembrolizumab) as a treatment option for relapsed/refractory Hodgkin lymphoma. [9]

MALIGNANT MELANOMA

Advanced (Unresectable or Metastatic) Melanoma Setting

- The efficacy of Keytruda (pembrolizumab) in malignant melanoma (unresectable or metastatic) is based on two, multi-center, open-label, pivotal clinical trials; one in Yervoy (ipilimumab)-refractory subjects and the other in Yervoy (ipilimumab)-naïve subjects.
    * One trial compared Keytruda (pembrolizumab) in doses of 10 mg/kg IV every 2 weeks or every 3 weeks with Yervoy (ipilimumab) 3 mg/kg IV every 3 weeks in progressive, unresectable, or metastatic disease. [8,18] Progression-free survival (PFS) and 12-month survival were superior in the Keytruda (pembrolizumab) treatment arms. Overall survival (OS) was not yet mature. [Note: The FDA-approved dosing of Keytruda (pembrolizumab) is 2 mg/kg IV every 3 weeks, so the applicability of these results is uncertain]
    * A second trial compared Keytruda (pembrolizumab) 2 mg/kg or 10 mg/kg IV every 3 weeks with investigator's choice of chemotherapy in progressive, unresectable, or metastatic disease. [8,19] There was a statistically significant improvement in median PFS with Keytruda (pembrolizumab) relative to the chemotherapy arm; however, the clinical relevance of the small numerical difference (0.2 months) is uncertain. There was no difference in PFS between the two Keytruda (pembrolizumab) dosing arms. Overall survival is not mature.
    * There is no evidence to date that Keytruda (pembrolizumab) has any clinical benefit (improved overall survival, symptom control, function, or quality of life) in melanoma. Additionally, much of the available evidence is for doses that are much higher than the FDA-approved dose of Keytruda (pembrolizumab).

Keytruda (pembrolizumab) as an Adjuvant Therapy for Resectable Melanoma

- Keytruda (pembrolizumab) was evaluated as an adjuvant therapy in patients with resectable stage IIIB/C or stage IV (metastatic) melanoma after complete surgical resection [KEYNOTE-054]. [20]
    * The study compared Keytruda (pembrolizumab) with placebo, dosed every 3 weeks for 18 cycles. Treatment was started within 13 weeks of tumor resection and was continued for up to one year.
    * There was a statistically significant improvement in recurrence-free survival (RFS) with Keytruda (pembrolizumab). It is unknown whether this will eventually translate to improvement in OS, a clinically relevant endpoint.
- Keytruda (pembrolizumab) was also evaluated as an adjuvant therapy for stage IIB and IIC (completely resectable) melanoma [KEYNOTE-716] where it was found to improve RFS and distant metastasis-free survival (DMFS) relative to placebo. [21] There is currently no

evidence of clinical benefit, such as improved OS. Since there is a high cure rate with complete resection alone in early melanoma the potential for introducing serious side effects with adjuvant immunotherapy should be carefully considered, particularly in the absence of clinical outcomes data.

  * Mature survival data are not expected for many years because the prognosis for these early-stage melanoma patients is good, and life expectancy is relatively long with five-year survival rates approaching 99%.
  * Based on preliminary results, fourteen patients would need to be treated with Keytruda (pembrolizumab) for one patient to avoid disease relapse within the first year; however, only seven patients would need to be treated for one patient to discontinue Keytruda (pembrolizumab) due to a severe AE by one year.

- NCCN melanoma guideline: Keytruda (pembrolizumab) is listed as an option for metastatic/unresectable melanoma (first-line or subsequent therapy) and in the adjuvant setting (after complete resection) for stage IIIB and IIIC disease. For stage IIB and IIC disease, observation and adjuvant Keytruda (pembrolizumab) are listed as recommendations. If Keytruda (pembrolizumab) is considered, the guideline states the need for careful assessment of risk versus benefit as there is currently no information evaluating its impact on overall survival in this population. [9]

MERKEL CELL CARCINOMA (MCC):

- Keytruda (pembrolizumab) was FDA-approved as a single agent for locally advanced or metastatic MCC, previously untreated with systemic therapy for advanced disease, based on a small, single-arm Phase 2 trial that evaluated tumor response rate [KEYNOTE-017]. [22]
- A clinically relevant benefit, such as improved OS relative to standard of care, has not been established. Phase 3 trials are ongoing. [23]
- Chemotherapy historically has been the standard approach for advanced MCC. Although MCC appears to be chemosensitive, the duration of response is limited. The impact of chemotherapy on survival in patients with metastatic MCC is unclear. [9]
- The NCCN guideline lists pembrolizumab among potential treatment options for unresectable MCC. [9]

NON-SMALL LUNG CANCER (NSCLC)

<u>Advanced (unresectable or metastatic) NSCLC</u>

- Keytruda (pembrolizumab) improves overall survival (OS) relative to cytotoxic chemotherapy in patients with metastatic NSCLC in the following treatment settings:
  * Front-line therapy for nonsquamous disease when administered with a platinum plus Alimta (pemetrexed) [KEYNOTE-021]. [24]
  * First-line therapy for squamous disease when administered with carboplatin plus a taxane [KEYNOTE-407]. [25]
  * First- or subsequent-line therapy for PD-L1-positive tumors [Tumor Proportion Score (TPS) $\geq$ 50% first-line; $\geq$ 1% subsequent] when used as a single agent [KEYNOTE-024, -010]. [26,27]

- An FDA-approved test (PD-L1 IHC 22C3 pharmDx) was developed in conjunction with Keytruda (pembrolizumab). The TPS measures the proportion of viable tumor cells that show partial or complete membrane staining on immunohistochemical (IHC) assay. [28]
- The NCCN NSCLC guideline recommends Keytruda (pembrolizumab) for: [9]
    * First-line, metastatic NSCLC when:
        - PD-L1 expression positive (≥ 50%) and tumor is EGFR-, ALK-, ROS1-, or BRAF-negative [category 1].
        - Nonsquamous histology: with a platin plus pemetrexed [category 1, preferred].
        - Squamous histology: with carboplatin plus paclitaxel or albumin-bound Abraxane (paclitaxel) [category 1, preferred].
    * Subsequent therapy for metastatic, PD-L1 expression positive (≥ 1%) NSCLC with ECOG performance status of 0, 1, or 2 [category 1].

Earlier stage NSCLC, resected - Adjuvant therapy

- Keytruda (pembrolizumab), as a single agent, demonstrated improved disease-free survival (DFS) relative to best supportive care in the adjuvant setting for patients with stage IB (T2a ≥4 cm), II, or IIIA NSCLC after complete tumor resection and standard adjuvant therapy with a platinum-based chemotherapy regimen, based on an interim analysis. [8,29]
    * Patients in the experimental arm received Keytruda (pembrolizumab) every 3 weeks for one year (up to 18 cycles) unless disease recurrence or unacceptable toxicity occurred.
    * Patients in the trial received a median of four cycles of adjuvant cisplatin-based chemotherapy after complete resection.
    * Prior use of PD-1/PD-L1 inhibitors was not allowed, such as in the neoadjuvant setting.
    * Although patients with TC >1% PD-L1 expression demonstrated a DFS benefit, patients with a high PD-L1 expression (TC ≥ 50%) appeared to have the most significant DFS benefit based on a pre-determined subgroup analysis.
    * DFS is not a validated endpoint in adjuvant NSCLC and has not been correlated to meaningful clinical outcomes such as overall survival.
- The NCCN NSCLC treatment guideline lists Keytruda (pembrolizumab) as an option in the adjuvant setting for completely resected stage II-IIIA NSCLC in patients who received previous adjuvant chemotherapy, with a footnote that the value of adjuvant therapy in PD-L1 negative NSCLC is unclear. [9]

Earlier stage NSCLC, resectable - Neoadjuvant therapy followed by adjuvant therapy

- An RCT [KEYNOTE-671] evaluated Keytruda (pembrolizumab) in resectable NSCLC as an add-on to platinum-containing chemotherapy used in the neoadjuvant setting (prior to surgical resection), and then continued as a monotherapy in the adjuvant setting (after surgical resection). [30]

    * Patients had pathologically confirmed stage II, IIIA, or IIIB NSCLC [involvement of ≥1 ipsilateral mediastinal lymph node or subcarinal lymph node (N2 stage)].
    * Keytruda (pembrolizumab) was given 200 mg every three weeks for 4 cycles (4 doses) prior to surgical resection, and then continued until disease progression or up to a maximum of 13 cycles (13 doses, as 200 mg every 3 weeks) after surgical resection.
    * The primary endpoint was event-free survival (EFS). The median EFS was not reached in the Keytruda (pembrolizumab) treatment arm and was 17 months in the placebo arm with a hazard ratio of 0.58 [95% CI: 0.46, 0.72] and p-value <0.001. OS results are not mature; however, no difference in OS has been detected to date.
- EFS is not a validated surrogate endpoint. It has not been shown to accurately predict significant improvement in clinical endpoints of interest such as OS and quality of life.
- Currently, another PD-1 inhibitor, Opdivo (nivolumab) is approved in this population as a neoadjuvant therapy (not continued as an adjuvant therapy). One of the outstanding questions from the Keytruda (pembrolizumab) study is the extent to which continuing a PD-1 inhibitor as an adjuvant therapy may (or may not) contribute to the efficacy of this longer regimen. Additional evidence, including impact on clinical outcomes, is needed. Trials of Opdivo (nivolumab) as neoadjuvant therapy followed by adjuvant therapy for resectable NSCLC are currently ongoing. Results are expected later in 2024.
- The NCCN NSCLC treatment guideline recommendations for resectable NSCLC include neoadjuvant Opdivo (nivolumab) plus platinum-doublet therapy for three cycles prior to surgical excision [preferred, cat 2A], and Keytruda (pembrolizumab) plus platinum-doublet therapy for four cycles prior to surgical resection followed by monotherapy for up to 13 cycles after surgical excision [preferred, cat 1]. [9]

PRIMARY MEDIASTINAL B-CELL LYMPHOMA (PMBCL)

- Keytruda (pembrolizumab) received FDA Accelerated approval for use in relapsed or refractory PMBCL based on tumor response rates from a single-arm, open-label study [KEYNOTE-170]. [8] To date, there is no evidence that it improves any clinically relevant outcome (e.g., improved survival, symptom control, function, or quality of life) in this disease setting.
    * Two small, uncontrolled, open-label studies evaluated patients with relapsed or refractory PMBCL who failed to achieve a complete remission after, or were ineligible for, an autologous stem cell transplant. [31-33]
    * Patients received a median of three prior therapies prior to Keytruda (pembrolizumab), and all had prior rituximab.
    * The reported objective response rate (ORR) was 45.3% and 47.6%. Six patients (11.3%) and seven patients (33.3%) had complete responses, respectively.
    * ORR has not been shown to accurately predict improvement in clinical endpoints in PMBCL.
- The NCCN B-cell lymphomas guideline lists rituximab-containing chemotherapy regimens among recommended therapy options for relapsed or refractory PMBCL when patients are

not candidates for high-dose therapies with stem cell rescue. Keytruda (pembrolizumab) is listed as a treatment option for relapsed disease. [9]

RENAL CELL CARCINOMA (RCC)

- FDA approval for Keytruda (pembrolizumab) in combination with Inlyta (axitinib) was based on interim PFS results from a phase 3, open-label (not blinded) randomized controlled trial (RCT) versus Sutent (sunitinib) monotherapy in patients with advanced, clear cell RCC in the front-line treatment [KEYNOTE-426]. [34] Overall survival, the co-primary endpoint, was not mature at the time of approval.
    * Median progression-free survival (PFS) was greater in the combination treatment arm [15.1 months versus 11.1 months with sunitinib].
    * Median overall survival was not met in either treatment arm at the time of the interim analysis.
    * In a subsequent analysis of overall survival, the median OS was not reached with pembrolizumab/axitinib and was 35.7 months in the sunitinib treatment arm. [35]
- There was a slight increase in grade 3 and 4 adverse effects in the combination arm. Additionally, 27% of subjects in the combination arm had immune-mediated AEs that required 40 mg or more per day of prednisone. [8]
- FDA approval of Keytruda (pembrolizumab) in combination with Lenvima (lenvatinib) is based on results from a phase 3, open-label (not blinded) RCT where this combination was found to show improved PFS relative to Sutent (sunitinib) monotherapy in patients with advanced, clear cell RCC in the front-line treatment [KEYNOTE-581/CLEAR Study]. [8,36]
    * All patients in the trial had a clear cell component (histology) and good performance status.
    * The median PFS was 23.9 months versus 9.2 months in the Keytruda (pembrolizumab)- Lenvima (lenvatinib) and Sutent (sunitinib) treatment arms, respectively.
    * Median OS was not met in either treatment arm.
    * Limitations of this study include, but are not limited to:
        - PFS is a surrogate radiographic endpoint that may not accurately predict that a patient will live a longer or better life.
        - Front-line therapies for advanced RCC have evolved such that Sutent (sunitinib) is no longer considered a standard of care. The efficacy and safety of Keytruda (pembrolizumab) plus Lenvima (lenvatinib) relative to other available standards of care is not known.
- The use of Keytruda (pembrolizumab) as an adjuvant therapy for patients with resected RCC with a high risk of recurrence was based on a RCT [KEYNOTE-564] that compared it with best supportive care. Keytruda (pembrolizumab) or placebo was given every 3 weeks for a maximum of 17 cycles (one year). [37]
    * Patients had either localized, resectable RCC; or had RCC with a fully resectable metastatic lesion [M1 No Evidence of Disease (NED)] and had a high risk of disease recurrence (refer to *Appendix 2* for definitions).

* Only patients with RCC with a clear cell component were included. No prior systemic therapy for RCC was allowed.
* The primary endpoint was disease-free survival (DFS), a non-validated endpoint. At 24 months, 77% and 68% of patients in the Keytruda (pembrolizumab) and placebo arms were alive and recurrence free, respectively. Overall survival data is not yet mature.

- Currently, there is no evidence supporting the use of Keytruda (pembrolizumab) in subsequent-line RCC settings, or as a monotherapy for advanced RCC.
- The NCCN kidney cancer guideline lists: [9]
  * The combination of Keytruda (pembrolizumab) with Inlyta (axitinib) or Lenvima (lenvatinib) among several recommended regimens as a first-line treatment for advanced, clear cell RCC. The recommendation ratings vary, based on risk assessment.
  * For resectable RCC with high risk of recurrence, Keytruda (pembrolizumab) as a single agent or surveillance are listed among recommendations for clear cell, previously untreated disease.

UROTHELIAL CARCINOMA (UC; BLADDER CANCER)

- ***As initial therapy (cisplatin ineligible) – Advanced disease -***

Monotherapy:

* A single-arm, open-label trial [KEYNOTE-052] evaluated Keytruda (pembrolizumab) in subjects with locally advanced or metastatic urothelial carcinoma who were ineligible for treatment with a cisplatin-based regimen. Approval was based on tumor response. [8,38]
  - ORR was 29%, with 7% of the responses considered complete.
  - Response rate was higher in patients with a combined positive score (CPS) $\geq$ 10%. [38]
  - There is no evidence that Keytruda (pembrolizumab) improves any clinically relevant outcome in this population. Although a median OS was reported, this information is of little relevance as there was no comparator group to allow any conclusion of a health benefit relative any other therapy.

In combination with Padcev (enfortumab vedotin):

* Padcev (enfortumab vedotin) was also evaluated as a front-line therapy for locally advanced or metastatic UC in combination with Keytruda (pembrolizumab) [Study EV-302/KEYNOTE-A39]. The evidence is based on a large (N=886), open-label RCT that compared this combination with a platinum-based chemotherapy regimen. [39]
  - Patients enrolled in the study had no prior therapy for advanced disease and were eligible to receive platinum-based chemotherapy. Prior neoadjuvant or adjuvant chemotherapy was allowed if there had been no disease recurrence within 12 months after its completion.

- Padcev (enfortumab vedotin) was given in 21-day cycles until disease progression. Keytruda (pembrolizumab) was given in 21-day cycles until disease progression or for a maximum of 35 cycles (2 years).
- Ninety-five percent of the population had metastatic disease. Approximately 27% had upper tract UC while the remaining 73% had lower tract UC.
- The median OS was 31.5 months and 16.1 months in the Padcev (enfortumab vedotin) plus Keytruda (pembrolizumab) and chemotherapy treatment arms, respectively.
- Although this trial included patients who were eligible to receive platinum-based chemotherapy, there is no evidence to establish superiority of this combination as compared to standard of care platinum-based chemotherapy followed by Bavencio (avelumab) maintenance. However, the use of the Padcev (enfortumab vedotin) plus Keytruda (pembrolizumab) is significantly more costly. In addition, the standard of care platinum-based chemotherapy followed by Bavencio (avelumab) maintenance is among the highest Category 1 recommended treatment options. Therefore, the use of Padcev (enfortumab vedotin) plus Keytruda (pembrolizumab) in patients who are eligible to receive platinum-based chemotherapy is considered 'not medically necessary.' As reflected in the coverage criteria, patients unable to receive platinum-based chemotherapy may be coverable for the combination of Padcev (enfortumab vedotin) plus Keytruda (pembrolizumab) in the first-line setting.

- ***As subsequent therapy - Advanced disease -*** A randomized, active-controlled, open-label trial [KEYNOTE-045] evaluated Keytruda (pembrolizumab) versus investigator's choice of single-agent chemotherapy in subjects with locally advanced or metastatic urothelial carcinoma who had disease progression on or after platinum-containing chemotherapy. [8,40]
  * Fifteen percent of subjects enrolled in the trial had disease progression following platinum-containing neoadjuvant or adjuvant chemotherapy.
  * The median OS was statistically greater with pembrolizumab vs. chemotherapy (10.3 months versus 7.4 months, respectively).
- ***For BCG-unresponsive non-muscle invasive bladder cancer (NMIBC) -*** A small, single-arm, non-blinded study evaluated Keytruda (pembrolizumab) in subjects with high-risk, recurrent or persistent NMIBC that was unresponsive to adequate treatment with Bacillus Calmette-Guerin (BCG) therapy who were either not eligible for a cystectomy (bladder removal), or did not elect to undergo cystectomy [KEYNOTE-057]. [8,41]
  * All patients had NMIBC with carcinoma *in situ* [stage Tis (63%), Ta (25%), or T1 (13%)].
  * Adequate BCG therapy was defined as having at least 5 of 6 induction intravesicular instillations AND either 2 of 3 maintenance instillations, or at least 2 of 6 doses of a second induction course. The median number of BCG instillations in the trial was 12.

* Complete response (CR) was the study endpoint and was achieved in 41% of patients. The median duration of response was 16.2 months. Overall response rate (ORR) is an unvalidated surrogate endpoint that has not been shown to accurately predict clinical outcomes.

- ***NCCN bladder cancer treatment guidelines*** recognize: [9]
  * *Front-line:* Category 1 recommendations for cisplatin-eligible patients include cisplatin plus gemcitabine followed by Bavencio (avelumab) maintenance, (Opdivo) nivolumab plus gemcitabine/cisplatin followed by (Opdivo) nivolumab maintenance, Padcev (enfortumab vedotin) plus Keytruda (pembrolizumab), and dose-dense methotrexate/vinblastine/doxorubicin/cisplatin followed by Bavencio (avelumab) maintenance therapy. Both Padcev (enfortumab vedotin) plus Keytruda (pembrolizumab), and dose-dense methotrexate/vinblastine/doxorubicin/ cisplatin followed by Bavencio (avelumab) maintenance therapy are also listed as category 1 recommendations for cisplatin-ineligible patients.
  * *Second- and subsequent-line:* Keytruda (pembrolizumab) after initial therapy with a platinum-containing regimen when used as monotherapy [preferred, category 1]; and Padcev (enfortumab vedotin) monotherapy is listed among several category 2A recommendations.
  * Ineligibility for cisplatin in the clinical trial was defined as CrCl 30 to 60 mL/min, poor kidney function (CrCl < 60 mL/min), poor performance status (≥2), significant hearing loss (≥ 25 dB), grade 2-4 peripheral neuropathy, heart failure, other comorbidities. [38] Ineligibility for cisplatin is mentioned in NCCN as renal impairment (CrCl < 60 mL/minute) or comorbidities. Ineligibility for any platinum-containing chemotherapy is not explicitly defined by the clinical trials or NCCN. However, NCCN notes that carboplatin can be substituted for cisplatin for patients with a CrCl < 60 mL/min. Overall comorbidities should be considered for platinum eligibility (such as cardiac disease, advanced age, performance status, or "if the patient is unfit").
  * In patients with NMIBC, the NCCN lists Keytruda (pembrolizumab) as a recommended option for recurrent or persistent disease unresponsive to BCG and the patient is ineligible for a cystectomy or chooses not to have one.

GASTRIC AND GASTROESOPHAGEAL JUNCTION (GEJ) ADENOCARCINOMA

HER2-positive gastric and GEJ adenocarcinoma:

- A multicenter, randomized, double-blind, placebo-controlled trial [KEYNOTE-811] evaluated the addition of Keytruda (pembrolizumab) to standard of care (SOC) trastuzumab plus chemotherapy relative to placebo plus SOC in patients with ***HER2-positive***, locally advanced unresectable, or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma. [8,42,43]
  * All patients enrolled in this study had no prior therapy for metastatic disease, no prior PD-1/PD-L1 inhibitor therapy and had good performance status (PS).
  * Patients received SOC trastuzumab plus chemotherapy [either CAPEOX (87%) or fluorouracil plus cisplatin (13%)] in addition to either Keytruda (pembrolizumab) or placebo.

* Approximately 87% of patients had a PD-L1 CPS of 1% or more.
* There was no difference in median OS between the Keytruda (pembrolizumab) and placebo treatment arms in the intent-to-treat population. A subgroup analysis suggests a significant improvement in median OS in the patients with PD-L1-expressing tumors (CPS ≥1). Based on this information, the FDA updated the indication for Keytruda (pembrolizumab) in HER2-positive, advanced/metastatic gastric or GEJ adenocarcinoma to limit use to the PD-L1 CPS ≥1 subpopulation.

HER2-negative gastric and GEJ adenocarcinoma:

- A second, similarly designed trial [KEYNOTE-859] evaluated Keytruda (pembrolizumab) as an add-on to SOC chemotherapy as a front-line therapy for ***HER2-negative***, locally advanced unresectable, or metastatic gastric or GEJ adenocarcinoma. [44]
  * As in the study above, all patients enrolled in this study had no prior therapy for metastatic disease, no prior PD-1/PD-L1 inhibitor therapy and had good PS.
  * Patients received SOC chemotherapy [either CAPEOX (86%) or fluorouracil plus cisplatin (14%)] in addition to either Keytruda (pembrolizumab) or placebo.
  * Approximately 78% of patients had a PD-L1 CPS of 1% or more and 35% had a CPS ≥10.
  * There was a significant improvement in median OS in the Keytruda (pembrolizumab) treatment arm relative to the placebo arm in the intent-to-treat population (12.9 months and 11.5 months, respectively). The difference in median OS was greater in the subgroups with high levels of PD-L1 expression suggesting results may have been driven by PD-L1 expression. The median OS in patients with tumors that had PD-L1 CPS ≥10 was 15.7 months and 11.8 months in the Keytruda (pembrolizumab) and placebo arms, respectively.

NCCN gastric/GEJ cancer guidelines

- The NCCN guideline recommendations for the front-line treatment of unresectable, recurrent, or metastatic gastric or GEJ cancer include: [9]
  * ***HER2-positive disease:*** Fluoropyrimidine/cisplatin plus trastuzumab is listed as a preferred, category 1 recommendation. Keytruda (pembrolizumab) may be added to this regimen for tumors with PD-L1 CPS≥1 (also a preferred, category 1 recommendation).
  * ***HER2-negative disease:*** Fluoropyrimidine/oxaliplatin plus Opdivo (nivolumab) for PD-L1 CPS ≥5, and fluoropyrimidine/oxaliplatin or cisplatin plus Keytruda (pembrolizumab) for PD-L1 CPS ≥10 are listed as preferred, category 1 recommendations. The Keytruda (pembrolizumab) combination therapy recommendation drops to category 2A for CPS ≥1, and to category 2B for CPS 1 to <10.

PD-L1 expressing and other gastric and GEJ adenocarcinomas:

- Keytruda (pembrolizumab) received Accelerated approval as a monotherapy for recurrent locally advanced or metastatic gastric or GEJ adenocarcinoma in tumors expressing PD-L1 (CPS ≥ 1) when disease progressed on or after two or more lines of therapy [KEYNOTE-059]. Subsequently, this indication was voluntarily withdrawn by the manufacturer because clinical benefit was not demonstrated in confirmatory trials. [8,45]

Therefore, use of Keytruda (pembrolizumab) in the subsequent-line advanced gastric and GEJ adenocarcinoma settings is considered investigational.

- Several other Keytruda (pembrolizumab) trials have also failed to establish clinical benefit in various gastric cancer settings:
    * Keytruda (pembrolizumab) in the second-line setting failed to meet the primary endpoints of PFS and OS as compared to paclitaxel in a phase 3 trial [KEYNOTE-061]. [46] All subjects had gastric/GEJ cancer with a PD-L1 CPS of 1 or higher that progressed on first-line chemotherapy with a platinum and fluoropyrimidine.
    * In the first-line setting, Keytruda (pembrolizumab), as a monotherapy or in combination with chemotherapy, failed to improve PFS and OS as compared to chemotherapy alone in a phase 3 trial [KEYNOTE-062]. [47] All subjects had gastric/GEJ cancer with a PD-L1 CPS of 1 or higher. Among patients with a CPS of ≥ 10, Keytruda (pembrolizumab) was numerically, but not statistically, superior to chemotherapy. Of note, 15% of patients in the control arm were treated with post-trial immune checkpoint inhibitors.

ESOPHAGEAL and GEJ CANCER

Front-line setting:

- A double-blind RCT [KEYNOTE-590] evaluated the addition of Keytruda (pembrolizumab) to standard front-line chemotherapy relative to placebo plus chemotherapy in patients with locally advanced or metastatic esophageal or gastroesophageal junction (GEJ) carcinoma. The coprimary endpoints were PFS and OS. [8,48]
    * The trial included patients with esophageal cancer with either squamous cell carcinoma or adenocarcinoma histology. GEJ cancers were included if they had an epicenter 1 to 5 centimeters above the GEJ.
    * Therapy was continued until disease progression, unacceptable toxicity, or for up to a maximum of two years.
    * Patients enrolled in the trial were not candidates for surgical excision of their tumor or for definitive chemoradiation (CRT) and had no prior treatment in the advanced disease setting. The majority (54%) of patients enrolled had tumors that had a PD-L1 CPS ≥ 10.
    * The median OS in the overall population was 12.4 months and 9.8 months in the Keytruda (pembrolizumab) and placebo treatment arms, respectively; and the median OS in the PD-L1 CPS ≥ 10 population was 13.5 months and 9.4 months, respectively. An exploratory analysis found there was no difference in median OS in the PD-L1 CPS < 10 population (10.5 months and 10.6 months, respectively), suggesting that efficacy of Keytruda (pembrolizumab) was being driven by PD-L1 expression.
- The NCCN guidelines list chemotherapy plus a platin plus Keytruda (pembrolizumab) among several recommended treatment options for unresectable locally advanced or metastatic esophageal or esophagogastric junction cancer, but limits the use of Keytruda (pembrolizumab) to tumors with PD-L1 CPS ≥ 10. [9]

Subsequent-line setting:

- Keytruda (pembrolizumab) was evaluated in a randomized, controlled trial in patients with recurrent locally advanced, or metastatic esophageal carcinoma who progressed on or after on prior systemic therapy [KEYNOTE-181]. [49] The trial included both squamous cell carcinoma (ESCC) and adenocarcinoma. However, the primary efficacy endpoint was OS in patients with ESCC, patients with tumors expressing PD-L1 CPS ≥10, and all randomized patients.
    * Keytruda (pembrolizumab) as a single agent was compared with investigator's choice of chemotherapy.
    * Patients with HER2/neu-positive disease were required to have received treatment with an approved HER2/neu targeted therapy [e.g., trastuzumab].
    * The primary analysis for this study was in the subgroup of patients with PD-L1 expressing ESCC (CPS ≥ 10) found an overall survival advantage with Keytruda (pembrolizumab) relative to cytotoxic chemotherapy. There was no survival difference between the groups when the intent-to-treat population was analyzed so the FDA-approval excluded PD-L1 negative tumors.
    * Subpopulations with tumor histologies other than ESCC (e.g., patients with esophageal adenocarcinoma) were not part of the primary analysis so are not included as part of the FDA indication.
    * Randomization was not stratified by PD-L1 status which is a potential limitation of this data.
- The NCCN esophageal cancer guideline lists Keytruda (pembrolizumab) as a preferred, recommended option for esophageal squamous cell carcinoma (ESCC) when used in the second-line setting for PD-L1-positive tumors with CPS ≥ 10. It is also a recommended option when used in the third or subsequent-line setting for PD-L1-positive tumors with CPS of ≥ 1. [9]

ENDOMETRIAL CANCER

- Keytruda (pembrolizumab) received Accelerated FDA-approval for use in patients with metastatic endometrial carcinoma, in combination with Lenvima (lenvatinib), in patients whose disease progressed on prior therapy in any treatment setting and curative surgery or radiation is not an option. It was approved in this setting based on a cohort of patients from a small, single-arm trial that evaluated tumor response rate [KEYNOTE-146). [50] Clinical benefit has not been established.
- The evidence supporting the use of Keytruda (pembrolizumab) as a single agent in unresectable or metastatic, MSI-H/dMMR endometrial carcinoma after progression on standard front-line therapies is of poor quality. It is derived from a multi-cohort, single-arm trial that reported tumor response rate as the endpoint [KEYNOTE-158]. There is currently no comparative data or information related to improvement in any clinical outcome. [51]
- Subsequently, Keytruda (pembrolizumab) was evaluated in a large (N=816), randomized, double-blind, placebo-controlled trial [NRG-GY018] as part of a front-line regimen for advanced endometrial cancer where it was found to improve PFS. [52]
    * Patients enrolled in the trial had no prior systemic therapy in the advanced disease setting, including no prior PD-1/PD-L1 inhibitor therapy.

    * Keytruda (pembrolizumab) was initiated in combination with carboplatin plus paclitaxel chemotherapy for six cycles and was then continued as a single agent until disease progression.
    * Patients in the Keytruda (pembrolizumab) treatment arm had improved median PFS relative to those who received placebo. This PFS benefit extended to both mismatch repair proficient and deficient tumors (pMMR and dMMR).
    * PFS has not been shown to accurately predict any beneficial clinical outcome (it is an unvalidated surrogate endpoint).
    * The overall survival data from this study are not mature; however, interim results have not yet detected any survival difference between treatment groups.
- The NCCN uterine cancer guideline, which includes endometrial carcinoma, lists many single-agent and combination chemotherapy regimens as recommended regimens, including Keytruda (pembrolizumab) plus Lenvima (lenvatinib) under "Useful in Certain Circumstances." Keytruda (pembrolizumab) as a single-agent is also listed among recommendations for MSI-H/dMMR endometrial tumors, and in the front-line setting when used in combination with carboplatin and paclitaxel (in either dMMR or pMMR tumors). [9]

CUTANEOUS SQUAMOUS CELL CARCINOMA (cSCC)

- Keytruda (pembrolizumab) was evaluated in a Single-arm, non-blinded, multi-cohort, phase 2 trial in patients with cSCC [KEYNOTE-629]. [53]
    * The cohort evaluated for the FDA accelerated approval included metastatic cSCC (55) and advanced recurrent disease in which is not curable with surgery or radiation.
    * All subjects had prior systemic therapy, and 87% had ≥ 2 prior therapies.
    * An ORR of 34% was reported, with 3.8% complete response (CR) and 30% partial response (PR). However, health outcomes are unknown.
- ORR is an unvalidated surrogate endpoint that has not been shown to accurately predict clinical outcomes. ORR is a measure of tumor size (visible by physical observation or on x-ray) and is a combination of complete and partial responses. In advanced disease, ORR may not be representative of disease that has traveled to lymph nodes of other parts of the body, so it may not be an accurate measure of clinical benefit.
- The NCCN lists Keytruda (pembrolizumab) among several potential therapy recommendations for cSCC that has recurred or metastasized (disease that is not curable with resection and/or radiation). [9]

ANAL SQUAMOUS CELL CARCINOMA (SCC)

- Although not FDA-approved for this use, Keytruda (pembrolizumab) and Opdivo (nivolumab) have been used in anal squamous cell carcinoma that is refractory to or recurs on front-line chemotherapy based on the lack of effective therapies for refractory disease. The majority of patients with anal SCC respond well to standard cytotoxic chemotherapy.
- Preliminary studies suggest these therapies have potential activity in this setting:

    * A manufacturer-funded study reported an ORR of 17% (all partial responses) in 24 patients with recurrent PD-L1-positive (> 1%) advanced anal SCC who received Keytruda (pembrolizumab). [54]
    * A National Institutes of Health (NIH) funded study reported an ORR of 24% (two complete and seven partial responses) in 37 patients with treatment refractory metastatic anal SCC who received Opdivo (nivolumab). [55]
    * Additional studies are needed to establish whether there is a lasting clinical benefit with these PD-1 inhibitors in this treatment setting. However, given the lack of treatment alternatives in a relatively small patient population, the use of Keytruda (pembrolizumab) and Opdivo (nivolumab) are considered medically necessary and coverable in chemotherapy-refractory disease.

- Both Keytruda (pembrolizumab) and Opdivo (nivolumab) are listed as treatment options for subsequent therapy for recurrent anal carcinoma in the NCCN guideline. [9]
- Given the lack of treatment alternatives in a relatively small patient population, the use of Keytruda (pembrolizumab) is considered medically necessary and coverable in chemotherapy-refractory disease.

BREAST CANCER

- *Advanced (locally advanced or metastatic) triple-negative breast cancer (TNBC):*

  FDA approval in TNBC is based on an RCT that studied the addition of Keytruda (pembrolizumab) to standard chemotherapy (paclitaxel, paclitaxel protein-bound, or gemcitabine and carboplatin) relative to chemotherapy alone (placebo arm) in patients with locally recurrent unresectable or metastatic TNBC who had not been previously treated with chemotherapy in the metastatic setting [KEYNOTE-355]. [56] In patients with PD-L1 CPS $\geq$ 10, the addition of Keytruda (pembrolizumab) to standard chemotherapy improved OS, relative to chemotherapy alone.
    * The trial enrolled patients regardless of their PD-L1 status. When it became apparent that there was no PFS difference between the treatment groups, the protocol was amended to change the primary analysis from all comers to the subpopulation with a PD-L1 combined positive score (CPS) $\geq$ 10.
    * In subjects with a PD-L1 CPS of $\geq$ 10, the median PFS was 9.7 months and 5.6 months in the Keytruda (pembrolizumab)/chemotherapy and chemotherapy only treatment arms, respectively. The secondary endpoint was PFS in the PD-L1 CPS $\geq$ 1 subgroup. No difference in PFS was demonstrated in this population.
    * A subsequent analysis reported a statistically significant improvement in median OS for the subpopulation with PD-L1 CPS $\geq$ 10. The median OS was 23.0 months and 16.1 months in the Keytruda (pembrolizumab)/chemotherapy and chemotherapy only treatment arms, respectively [HR 0.73 (95% CI: 0.55, 0.95)]. There was no difference in OS detected between the Keytruda (pembrolizumab) and placebo groups in the subgroup with PD-L1 CPS $\geq$ 1 or in the ITT population ('All comers' regardless of PD-L1 status). [57]
    * NCCN guidelines list the use of Keytruda (pembrolizumab) among recommended therapies for PD-L1-positive advanced TNBC. [9]

- *Neoadjuvant/adjuvant triple-negative breast cancer (TNBC)*:

  FDA approval of Keytruda (pembrolizumab) in combination with chemotherapy as a neoadjuvant therapy and then continued as a single agent as an adjuvant therapy after surgical excision was based on a double-blind, placebo-controlled RCT that compared pembrolizumab (plus chemotherapy) with placebo (plus chemotherapy) and evaluated event-free survival (EFS) as a surrogate endpoint. [KEYNOTE-522] [8,58] The health benefit of the addition of Keytruda (pembrolizumab) to chemotherapy relative to alternatives (chemotherapy alone) for early TNBC is currently unknown. The OS data is not yet mature and EFS is not a validated endpoint for predicting an OS benefit.

  * Patients had newly diagnosed early-stage, high-risk TNBC who had no prior systemic therapy for their disease and were newly diagnosed. Patients with metastatic disease were excluded from the study.
  * Keytruda (pembrolizumab) was given with chemotherapy for eight total 3-week cycles prior to surgical excision and was continued as monotherapy as a single agent for up to 9 additional, 3-week cycles [total of up to one year of Keytruda (pembrolizumab)].
  * There was a relative improvement in EFS reported for patients in the Keytruda (pembrolizumab) arm of the study in a preliminary analysis. OS data is not currently mature.
  * EFS is not a validated endpoint for predicting an OS benefit. Therefore, it is not currently known if Keytruda (pembrolizumab) contributes to a better or a longer life when used in this setting. Results from a future OS analysis are needed to confirm clinical benefit (OS data is not mature).
    - The FDA allows the use of EFS as a surrogate marker for the approval of drugs in early-stage breast cancer; however, its accuracy in predicting clinically relevant outcomes is controversial. [59] This scenario is analogous to the use of PFS (another radiographic surrogate endpoint) for drug approvals for advanced breast cancer where several medications were found to improve PFS without confirmation of any clinical benefit in follow up trials.
    - A recent publication analyzed EFS as a surrogate for OS in early breast cancer. The analysis included 7 studies for this surrogacy analysis. The authors concluded that although EFS moderately correlated with improved OS in early breast cancer in the neoadjuvant setting, the confidence intervals are wide, and the association was not significant. [59]
  * The current NCCN guidelines list the use of adjuvant or neoadjuvant Keytruda (pembrolizumab) among potential treatment options for early-stage, high-risk TNBC. [9]

OTHER INVESTIGATIONAL USES

- Keytruda (pembrolizumab) is actively being studied to determine if there is benefit in treating other types of cancers including multiple myeloma (MM), and ovarian cancer. To date, studies are preliminary and ongoing and the risk versus potential for clinical benefit remains under investigation. [23]

- *Vulvar Cancer*
  * The evidence for Keytruda (pembrolizumab) in vulvar cancer is limited to an ongoing, single-arm, basket study (KEYNOTE-158) in multiple types of solid tumors. The cohort of patients with metastatic and/or unresectable vulvar squamous cell carcinoma consisted of 101 patients. The tumor response rate for this cohort was 10.9% with only 1 complete response. There is no comparative evidence or outcomes data available in this population. [60]
  * The NCCN vulvar cancer guideline lists Keytruda (pembrolizumab) as a potential biomarker-directed systemic therapy for recurrent or metastatic vulvar cancer for tumors that are TMB-H, MSI-H/dMMR, or PD-L1 (CPS) $\geq$ 1. [9]
- *MSI-H Tumors (other than CRC and endometrial carcinoma)*
  * Keytruda (pembrolizumab) is FDA approved as a treatment option for patients with any progressive MSI-H/dMMR solid tumor ("tumor agnostic") when no satisfactory treatment alternatives are available. [8] However, currently there is insufficient evidence to establish the efficacy or safety of Keytruda (pembrolizumab) in patients with other MSI-H/dMMR tumors. [8,61,62]
  * The Accelerated approval of Keytruda (pembrolizumab) for MSI-H or dMMR tumors was based on preliminary tumor response [overall response rate (ORR)] and duration of response (DOR) data from a "basket trial" pooled analysis of 149 patients across five different early phase, open-label trials (90 patients with CRC and 59 non-CRC patients). [61,63]
  * Subjects enrolled in the trial had advanced solid tumors and at least one prior chemotherapy regimen.
    - This tumor agnostic approval includes use in many cancer types that were either not tested in the "basket trial" or were only tested in very low numbers (n < 14) of patients.
    - Fourteen types of solid tumors were represented in the non-CRC cohort of 59 patients. Nine tumor types were represented by only one or two patients.

      No patients with uterine cancer (leiomyosarcoma) were represented in the sample.
  * Subsequently, one non-randomized, single-arm Phase 2 trial evaluated Keytruda (pembrolizumab) for non-CRC MSI-H/dMMR solid tumors.
    - The trial enrolled 233 patients with 27 tumor types.
    - Similar to the basket trial above, ORR was used as the primary endpoint.
    - An ORR of 34% was reported. However, health outcomes are unknown.
    - Endometrial cancer was the most common tumor type (n=49), followed by gastric (n=24), and cholangiocarcinoma (n=22). However, insufficient details were reported to establish if the endometrial tumors were sufficiently treated with standard therapies ("treatment alternatives").
  * Although reported tumor response rates appear promising, it is not known if Keytruda (pembrolizumab) improves tumor response in all MSI-H/dMMR solid tumors, or positively impacts any clinically relevant outcome. Confirmatory studies

are necessary to establish clinical benefit. Therefore, the use of Keytruda (pembrolizumab) for MSI-H/dMMR tumors (other than CRC and endometrial carcinoma, or as detailed in the coverage criteria) is considered investigational.

- *Ovarian cancer*:
  * The evidence for the use of Keytruda (pembrolizumab) is limited to a non-randomized, non-comparative phase 2 trial for advanced recurrent ovarian cancer [KEYNOTE-100]. [64] Although this initial evidence of overall response rate (ORR) is promising, along with other posters reporting single-arm data, there is insufficient data at this time to establish an improvement in clinically meaningful endpoints in ovarian cancer such as survival or quality of life. Therefore, the use of Keytruda (pembrolizumab) for ovarian cancer is considered investigational.
- *Sarcoma (including STS, osteosarcoma)*:
  * There is interest in the use of Keytruda (pembrolizumab) for various soft tissue sarcomas (STS) including liposarcoma, as well as osteosarcoma.
  * Keytruda (pembrolizumab) is included in the NCCN STS guidelines as an option for salvage therapy for certain types of STS, such as undifferentiated pleomorphic sarcoma (UPS). [9] However, the recommendation is based on one phase 2 trial in STS and osteosarcoma which did not meet the primary endpoint. [65]
  * A second trial in osteosarcoma also did not meet the primary endpoint. [66] Additional trials are ongoing. [23] Therefore, the use of Keytruda (pembrolizumab) for STS and osteosarcoma is considered investigational.
- *Small cell lung cancer (SCLC)*:
  * Keytruda (pembrolizumab) received Accelerated approval for metastatic SCLC, based on cohort of patients from single-arm, open-label trials that evaluated tumor response rates as an endpoint with pretreated metastatic (after a platinum-based chemotherapy and at least one other prior systemic regimen). [8,67]
  * However, subsequent trials [KEYNOTE-604] failed to demonstrate a proven health benefit and the company withdrew the FDA indication. [68] Therefore, the use of Keytruda (pembrolizumab) for SCLC is considered investigational at this time.
- *Tumor mutational burden-high (TMB-H) solid tumors*
  * Keytruda (pembrolizumab) received Accelerated FDA approval in patients with solid tumors that have high tumor mutational burden (TMB-H, based on genetic testing) and who have no remaining satisfactory treatment options, based on a 'basket trial' in a small number of patients with tumors that were found to be TMB-H. [8,69] Accelerated approval means that no clinical benefit has yet been demonstrated. The available evidence is of very poor quality. Additional clinical trials are needed to establish clinical benefit.
    - Patients were enrolled based on having TMB-H solid tumors. Inclusion was independent of tumor type or site. Pembrolizumab was given and tumor

size monitored using x-rays, for overall response rate (ORR).

- Small sample size, heterogeneity of tumor types, and lack of clinical outcomes limit interpretation of the data for estimation of clinical benefit.
  - A very small number of types of tumors were represented, only nine at the time of the initial data cut. ORR varied widely across tumor types with some types showing no response (e.g., salivary, thyroid, and mesothelioma).
  - ORR has not been shown to accurately predict clinical benefit such as improved survival, quality of life, or symptom control.
- A high tumor mutational burden (TMB-H) was defined as having 10 or more mutations per megabase (mut/Mb) as determined by the FoundationOne CDx panel. The selection of 10 mut/Mb as a cutoff for administration of Keytruda (pembrolizumab) is arbitrary. Use of this definition is not associated with improvement in any clinically important outcome. Furthermore, this definition is based specifically on the FoundationOne CDx genetic test. Since there is no current standard for determining TMB-high status across different genetic tests, selection of appropriate patients may be confounded.
- TMB is heterogeneous both within and across different tumor types. The extrapolation of this evidence from this small sample of tumors across all tumor types is not a valid predictor of potential for benefit.

* The NCCN compendium generally aligns with the FDA label and recommends Keytruda (pembrolizumab) in TMB-high tumors when there are no other treatment options. [70] However, for the reasons stated above, the use of Keytruda (pembrolizumab) in TMB-H tumors is considered investigational.

Dosing [8]

- Keytruda (pembrolizumab) is administered via intravenous (IV) infusion as follows:
  * ***Earlier stage disease, resected (or planned resection)***
    - ***Earlier-stage NSCLC neoadjuvant/adjuvant setting:*** neoadjuvant treatment with Keytruda (pembrolizumab) in combination with chemotherapy for up to 12 weeks (four doses of 200 mg every 3 weeks) or until disease progression or unacceptable toxicity, followed by surgery (within 20 weeks of starting neoadjuvant therapy), then followed by adjuvant treatment with Keytruda (pembrolizumab) [starting between 4 to 12 weeks after surgery] as a single agent for up to 39 weeks (13 doses of 200 mg every 3 weeks) or until disease recurrence or unacceptable toxicity.
    - ***Early-stage TNBC neoadjuvant/adjuvant setting***: neoadjuvant treatment with Keytruda (pembrolizumab) in combination with chemotherapy for 24 weeks (8 doses of 200 mg every 3 weeks or 4 doses of 400 mg every 6 weeks) or until disease progression or unacceptable toxicity, followed by surgery (3 to 6 weeks after the last neoadjuvant cycle), followed by adjuvant treatment with Keytruda (pembrolizumab) as a single agent for up to 27 weeks (9 doses of 200 mg every 3 weeks or 5

doses of 400 mg every 6 weeks) or until disease recurrence or unacceptable toxicity.

- ***Adjuvant melanoma setting:*** Doses up to 200 mg every 3 weeks until disease progression, for up to a maximum of 18 cycles (12 months, 54 weeks). There is no evidence to establish the efficacy of use beyond 54 weeks in patients with resected melanoma.
- ***Adjuvant RCC setting:*** Doses up to 200 mg every 3 weeks until disease progression, for up to a maximum of 17 cycles (51 weeks). There is no evidence to establish the efficacy of use beyond 51 weeks in patients with resected RCC.
- ***Adjuvant NSCLC setting:*** Doses up to 200 mg every 3 weeks until disease progression, for up to a maximum of 18 cycles (54 weeks). There is no evidence to establish the efficacy of use beyond 54 weeks in patients with resected NSCLC.

* ***Advanced Disease/Stages (unresectable)***

- ***Melanoma (unresectable or metastatic)***: 200 mg IV every 3 weeks until disease progression.
- ***Most all other indications***: 200 mg IV every 3 weeks until disease progression, intolerable AEs, or for up to 24 months in the absence of disease progression.
- ***Hodgkin lymphoma or PMBCL, pediatrics***: 2 mg/kg (up to 200 mg per dose) IV every 3 weeks until disease progression, intolerable adverse events, or for up to 24 months in the absence of disease progression.

* ***Consolidated dosing***: pembrolizumab may be dosed 400 mg every 6 weeks for many labeled indications.

* ***Dose interruptions:*** For patients who have the course of therapy interrupted or doses delayed, dose authorization periods (date range of the authorization) may be extended to allow the full course (such as 12- or 24-months) to be completed, not to exceed the number of doses that would be given in a contiguous period.

* ***Dosing beyond 24 months***: Most Keytruda (pembrolizumab) trials were specifically designed to administer a 24-month treatment course, at which time therapy was stopped and patients observed. However, in clinical practice, ongoing therapy (beyond 24 months) may be warranted in patients with advanced/metastatic disease who have a partial response to, and overall disease stability on Keytruda (pembrolizumab). Per the policy "Quantity limits," pembrolizumab is coverable only "until disease progression." Therefore, use beyond 24 months will not be authorized for patients with documented disease progression.

Appendix 1: FDA-approved PD-1 and PD-L1 blocking monoclonal antibody therapies [a]
Programmed death receptor-1 (PD-1) inhibitors
Jemperli (dostarlimab)
Keytruda (pembrolizumab)
Libtayo (cemiplimab-rwlc)
Loqtorzi (toripalimab)
Opdivo (nivolumab)
Tevimbra (tislelizumab)
Zynyz (retifanlimab)
Programmed death-ligand 1 (PD-L1) inhibitor
Bavencio (avelumab)
Imfinzi (durvalumab)
Tecentriq (atezolizumab)

[a] Or as listed on the FDA.gov website.

Appendix 2: Definition for High-Risk of Renal Cell Carcinoma (RCC) Recurrence [37]
Intermediate-High Risk
- pT2, Grade 4 (histology) or sarcomatoid, N0, M0 (nodes negative, no metastases) **OR** - pT3, Any Grade (histology), N0, M0 (nodes negative, no metastases)
High-Risk
- pT4, Any Grade 4 (histology), N0, M0 (nodes negative, no metastases) **OR** - pT Any Stage, Any Grade (histology), N+, M0 (nodes positive, no metastases)
M1 No Evidence of Disease (NED)
RCC is present not only with the primary kidney tumor but also solid, isolated, soft tissue metastasis that can be completely resected at the time of nephrectomy

T = tumor; N = lymph nodes; M = metastases

Cross References
Molecular Analysis for Targeted Therapy of Non-Small Cell Lung Cancer (NSCLC), Medical Policy Manual, Genetic Testing Policy No. 56
Adcetris, brentuximab vedotin, Medication Policy Manual, Policy No. dru264
Bavencio, avelumab, Medication Policy Manual, Policy No. dru499
BRAF inhibitors, Medication Policy Manual, Policy No. dru728
Imfinzi, durvalumab, Medication Policy Manual, Policy No. dru500
Inlyta, axitinib, Medication Policy Manual, Policy No. dru273
Jemperli, dostarlimab, Medication Policy Manual, Policy No. dru673
Lenvima, lenvatinib, Medication Policy Manual, Policy No. dru398
Libtayo, cemiplimab-rwlc, Medication Policy Manual, Policy No. dru565
Loqtorzi, toripalimab, Medication Policy Manual, Policy No. dru774
Mitogen-activated extracellular signal-related kinase (MEK) inhibitors, Medication Policy Manual, Policy No. dru727
Opdivo, nivolumab, Medication Policy Manual, Policy No. dru390
Padcev, enfortumab vedotin, Medication Policy Manual, Policy No. dru622
Tecentriq, atezolizumab, Medication Policy Manual, Policy No. dru463
Tevimbra, tislelizumab, Medication Policy Manual, Policy No. dru785
Yervoy, ipilimumab, Medication Policy Manual, Policy No. dru238
Products with Therapeutically Equivalent Biosimilars/Reference Products, Medication Policy Manual, Policy No. dru620

Codes	Number	Description
HCPCS	J9271	Injection, pembrolizumab (Keytruda), 1 mg

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Revision History

Revision Date	Revision Summary
9/19/2024	• Broadened coverage criteria for front-line use in combination with carboplatin and paclitaxel in advanced or recurrent endometrial carcinoma to extend to mismatch repair proficient (pMMR) tumors based on emerging evidence in this population which resulted in an expanded FDA indication. • Updated and made language pertaining to advanced disease settings more consistent across the different covered uses (no change to the intent of the policy). • Reorganized criteria under Urothelial Carcinoma to improve the ease of administration (no change to the intent of the policy) • Changed '6 months' to '24 weeks' in criteria III.C. and III.D. for consistency across the policy (no change to the intent of the policy).

Revision Date	Revision Summary
6/20/2024	**Effective 7/15/24:** • Added coverage for locally advanced, FIGO 2014 stage III to IVA cervical cancer with squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma for newly diagnosed (untreated) disease when used in combination with chemoradiation. [new indication] • Updated coverage criteria for Keytruda (pembrolizumab) when used in combination with trastuzumab and chemotherapy for locally advanced or metastatic HER2-positive gastric or GEJ in an addition that tumor PD-L1 CPS is >1 based on updated results showing predominance for benefit in this subpopulation. [newly modified FDA indication] • Added coverage for Keytruda (pembrolizumab) when used in combination with chemotherapy for locally advanced or metastatic HER2-negative gastric or GEJ when there has been no prior systemic therapy in the advanced disease setting [new indication]. A criterion was also added to restrict use to tumors with PD-L1 CPS ≥1 based on results suggesting results were driven by this subpopulation. • Added coverage for Keytruda (pembrolizumab) as a front-line therapy for unresectable locally advanced or metastatic biliary tract cancer (BTC) when used in combination with gemcitabine and cisplatin. [new indication] • Updated hepatocellular carcinoma (HCC) criteria by limiting coverage to HCC secondary to hepatitis B virus infection and document Child-Pugh Class A based on a recently completed pivotal trial. The step therapy requirement was updated to make it less specific ('one prior systemic therapy') to reflect changing standards of care over time. [newly modified FDA indication] • Added coverage for Keytruda (pembrolizumab) as a neoadjuvant therapy (in combination with platinum-containing therapy for up to four doses), followed by adjuvant therapy (as monotherapy) for up to 13 additional doses when used for stage II, IIIA, or IIIB non-small cell lung cancer (NSCLC). [new indication] • Updated criteria for Keytruda (pembrolizumab) in locally advanced unresectable or metastatic urothelial carcinoma (UC) to clarify that the patient has not had prior systemic therapy in the advanced disease setting (no change to intent). • Updated 'Quantity limits and Authorization' section to include information for the new indications added above.

Revision Date	Revision Summary
12/7/2023	• Added coverage criteria for adjuvant use in stage IIB and IIC melanoma and removed use in this population from the list of investigational uses. • Added coverage for use as part of a front-line regimen for unresectable endometrial cancer when given in combination with carboplatin/ paclitaxel for dMMR or MSI-H tumors based on evidence that is similar to that for Jemperli (dostarlimab) in this population. • Updated the criteria related to tumor staging under NMIBC to parallel the criteria for Adstiladrin (nadofaragene firadenovec) based on the Keytruda (pembrolizumab) study population and their similar placement in guidelines. • Updated reauthorization criteria to allow for a shortened authorization length for noted potential disease progression.
9/14/2023	Added coverage criteria for use in locally advanced or metastatic urothelial carcinoma when used in combination with Padcev (enfortumab vedotin) as a front-line therapy for patients who are not eligible for cisplatin-containing chemotherapy.
6/15/2023	• Added coverage for adjuvant use in resected NSCLC aligned with label, a newly approved FDA indication. • Updated *Table 1* for Quantity Limits: Earlier stage disease, resected or planned resection (neoadjuvant/adjuvant use) versus advanced disease (unresectable).
12/9/2022	• Deleted requirement that Keytruda (pembrolizumab) be used as monotherapy for relapsed/refractory cHL. • Updated standard language in policy.
7/14/2022	Updated Table 1 to clarify coverable duration of therapy for recurrent/metastatic TNBC and updated wording for operational ease of administration.
6/17/2022	• Added coverage for the following newly FDA approved indications: - Adjuvant use in resected renal cell carcinoma (RCC) with a clear cell component and a high risk of recurrence when there has been no prior systemic therapy. - MSI-H/dMMR endometrial carcinoma after at least one prior systemic therapy. *Note: Removed from list of investigational uses.* • Added adjuvant use in stage IIB and IIC melanoma as investigational.
3/18/2022	Added coverage criteria for high-risk, early-stage TNBC and removed it from the "Not Medically Necessary" section.

Revision Date	Revision Summary
10/15/2021	**Effective 11/15/21:** • Added coverage criteria for newly FDA approved indications: - Front-line use in advanced, HER2-positive gastric and GEJ cancer when used as an add-on to trastuzumab plus chemotherapy - Front-line use in advanced esophageal or GEJ cancer when patient not candidate for surgical resection or definitive chemoradiotherapy, PD-L1 CPS > 10, and given in combination with a platinum plus fluoropyrimidine - Advanced RCC when used in combination with Lenvima (lenvatinib). - Early-stage, high-risk TNBC will be considered 'not medically necessary' and therefore not covered because clinical benefit not yet established. • Added coverage in advanced triple negative breast cancer (TNBC) as first-line therapy in combination with chemotherapy when PD-L1 CPS > 10 based on newly available overall survival data. • Updated coverage in cervical cancer to cover in front-line setting when PD-L1 CPS > 1 when administered in combination with front-line chemotherapy based on newly available overall survival data. • Simplified criteria for endometrial carcinoma criteria to be agnostic to combination therapy. • Removed coverage for use as a third- or subsequent-line therapy for advanced gastric cancer with PD-L1 CPS > 1 because clinical benefit was not shown in confirmatory trials and the indication withdrawn by manufacturer. **Effective 2/1/22:** Change reauthorization from 'may' to 'shall.' Operationally, all approvals will be for six months. Ongoing therapy (beyond six months) will be subject to reauthorization review every six months, for documentation of disease stability or improvement and lack of disease progression.

Revision Date	Revision Summary
4/21/2021	• Added coverage criteria for cSCC, a newly approved FDA indication (effective 5/15/2021). • Added PD-L1-expressing locally advanced unresectable/metastatic TNBC to 'Not Medically Necessary' uses, given the lack of benefit over coverable treatment alternatives (effective 5/15/2021). • Simplification of criteria for cHL and CRC MSI-H criteria (new expanded FDA indications). • Simplified criteria for: GEJ, HNSCC, melanoma, PMBCL, NSCLC, UC/NMIBC, and endometrial carcinoma, for operational clarity (no change to intent). • Reformat of coverage criteria to table format. • Clarified step therapy intent for HCC to HCC-TKI, including Lenvima (lenvatinib). • Removed coverage criteria for SCLC (FDA indication withdrawn). • Updated quantity limitations for new indications. • Updated 'Investigational uses' (added SCLC).
10/28/2020	Updated policy with new TMB-H indication. This indication is considered an 'investigational use' due to the very low quality of the evidence and the lack of proven benefit.
6/15/2020	• Removed references to brand Avastin, Herceptin, and Rituxan from policy to account for upcoming changes in biosimilars policy (dru620). • Added triple-negative breast cancer (TNBC) neoadjuvant/adjuvant data to the "Investigational Uses" section.
4/22/2020	Added coverage criteria for non-muscle invasive bladder cancer (NMIBC), a new FDA indication.
1/22/2020	• Added continuation of therapy (COT) criteria. • Simplified coverage criteria for NSCLC (metastatic disease and no prior checkpoint inhibitor therapy) • Added coverage for the following new coverable uses: SCLC, esophageal cancer, use in the front-line treatment of HNSCC (previously covered only as a subsequent-line therapy), endometrial cancer [in combination with Lenvima (lenvatinib)], and anal SCC - an off-label use, based on the lack of other treatment options and emerging preliminary evidence. • Simplified coverage criteria for resectable melanoma. • Updated quantity limitation section with new indications.
7/24/2019	Updated policy with criteria for coverage in front-line RCC, a new FDA-approved indication; and removed RCC from the list of investigational conditions (effective 8/15/2019).

Revision Date	Revision Summary
4/25/2019	• Added coverage for squamous metastatic NSCLC in combination with chemotherapy, hepatocellular carcinoma (after sorafenib), and adjuvant treatment of melanoma following complete resection (new indications; effective 07/01/2019). • Updated coverage criteria for NSCLC, for ease of administration. • Updated coverage criteria for Merkel Cell Carcinoma, for consistency.
1/8/2019	• Added coverage for metastatic cervical cancer and recurrent or refractory PMBCL (new indications). • Updated quantity limits to include the new indications. • Updated formatting (no change to content/intent).
7/20/2018	• Updated criteria under urothelial carcinoma to clarify coverage in the front-line setting for cisplatin-ineligible patients only when PD-L1 expressing and any platinum-ineligible patients, regardless of PD-L1 expression.
4/20/2018	• Added coverage criteria for gastric or gastroesophageal adenocarcinoma. • Aligned coverage in Hodgkin lymphoma with Opdivo coverage criteria. • Updated quantity limits to include new indication. • Clarified authorization is valid "until disease progression" (no change to intent). • Updated list of conditions considered investigational.
10/13/2017	• Added criteria for one new indication: MSI-H colorectal cancer. • Updated covered quantity for this new indication. • Updated uses considered investigational.
6/9/2017	• Added criteria for three new indications: classical Hodgkin lymphoma, urothelial carcinoma, and combination use with chemotherapy in the front-line treatment of metastatic nonsquamous NSCLC. • Updated covered quantities and durations for these new indications.
3/10/2017	• Clarified NSCLC criteria such that prior use of a PD-L1 inhibitor precludes coverage. • A maximum of 24 months of therapy was defined for use in NSCLC based available evidence and FDA-labeling.
2/17/2017	• Added coverage criteria for metastatic NSCLC in the first-line treatment setting. • Updated quantity limits for NSCLC based on new FDA-labeled dosing.

Revision Date	Revision Summary
11/11/2016	• Added coverage criteria for recurrent or metastatic HNSCC, a newly approved indication for Keytruda (pembrolizumab). • Updated quantity limits to reflect new dosing in HNSCC. • Lowered the level of PD-L1 expression required in the subsequent-line metastatic NSCLC setting based on updated package labeling. • Added first-line use of pembrolizumab in metastatic NSCLC, a new FDA indication, as not medically necessary. • Updated uses considered investigational. • Updated Appendices and cross-referenced policies.
3/11/2016	• Added coverage criteria for metastatic NSCLC, a newly approved indication for Keytruda (pembrolizumab). • Combined several appendices and added additional information pertaining to NSCLC.
12/11/2015	• Clarified that sequential therapy of PD-1 inhibitors (Opdivo/Keytruda) is not a covered use. • Add Appendix 1, with a list of available PD-1 inhibitors. • Add Appendix 3, with a list of other targeted therapies for melanoma.
11/13/2014	New policy.

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Medication Policy Manual

Policy No: dru382

Topic: Alpha-1 proteinase inhibitors:
- Aralast NP
- Glassia
- Prolastin-C
- Zemaira

Date of Origin: December 12, 2014

Committee Approval Date: June 20, 2024

Next Review Date: 2024

Effective Date: October 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Alpha-1 proteinase inhibitors (Aralast NP, Glassia, Prolastin-C and Zemaira) are IV administered preparations containing alpha-1 antitrypsin (A1AT), a naturally occurring enzyme purified from human blood. They are used in the treatment of alpha-1 antitrypsin deficiency (AATD), a rare genetic disorder that can lead to disease of the lungs (emphysema).

Policy/Criteria

Most contracts require pre-authorization approval of alpha-1 proteinase inhibitors (Aralast NP, Glassia, Prolastin-C, Zemaira), prior to coverage.

I. Continuation of therapy (COT): Alpha-1 proteinase inhibitors may be considered medically necessary for COT when criterion A AND B below are met.

A. One of the following (1, 2, or 3):

1. For diagnoses NOT listed in the coverage criteria below, full policy criteria must be met for coverage.

OR

2. For diagnoses listed in the coverage criteria below, criteria a and b must be met:

a. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

b. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

3. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

AND

B. Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, Site of Care Review, dru408].

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Alpha-1 proteinase inhibitors may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes), that criteria A through D below are met.

A. The diagnosis was established by, or in consultation with, a pulmonologist.

AND

B. A confirmed diagnosis of **alpha-1 antitrypsin deficiency (AATD) outflow obstruction (emphysema)** and one of the following (1 or 2):

1. FEV_1 (post bronchodilation) between 30-65%.

OR

2. Rapid decline in lung function, defined as a FEV_1 decline of more than 120ml over 12 months.

AND

C. Pretreatment alpha-1 antitrypsin (AAT) serum level less than 11 micromol/L (less than 80 mg/dL measured by radial immunodiffusion or less than 50mg/dL measured by nephelometry).

AND

D. Are negative for the MZ genotype of alpha-1 antitrypsin deficiency.

AND

E. Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, Site of Care Review, dru408].

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers alpha-1 proteinase inhibitors coverable only under the medical benefit (as provider-administered medications).

B. When pre-authorization is approved, alpha-1 proteinase inhibitor doses up to 60 mg/kg every week will be authorized.

C. Authorization **may** be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

IV. Use of an alpha-1 proteinase inhibitors is considered investigational when used for all other conditions, including but not limited to:

A. AATD without airflow obstruction (without emphysema), such as AATD-related liver disease or other AATD-related complications.

B. Use in patients with the MZ genotype of AATD.

C. Use in combination with other alpha1-proteinase inhibitor products.

Position Statement

- All alpha-1 proteinase inhibitor (alpha1-PI) products (Aralast NP, Glassia, Prolastin-C, and Zemaira) appear to be similar in biologic activity for slowing progression of emphysema in patients with alpha-1 antitrypsin deficiency (AATD).
- Although the overall net health benefit of alpha1-PI therapy is uncertain, treatment options for patients with moderate to severe emphysema are limited to symptomatic management, aside from lung transplantation.
- There is no evidence of clinically meaningful differences in safety or efficacy between alpha1-PI products. They vary in their reconstitution, time of infusion and storage, and have slight differences in protein composition and chemical structures; however, these differences have not been linked to specific clinical outcomes.
- Consensus guidelines recommend use of alpha1-PI replacement therapy ("augmentation therapy") for treatment of patients WITH airflow obstruction from AATD, but do not differentiate between products.
    * Patients with heterozygous phenotypes should not be treated with alpha1-PIs if the AAT level exceeds 11 micromol/L.
    * Patients with the MZ genotype are not recommended to be treated with alpha-PI's.
    * Guidelines recommend augmentation therapy in patients with an FEV_1 between 30% and 65% or those experiencing a rapid decline in lung function (>120ml/year).
        - There is no high-quality evidence to establish the efficacy of augmentation therapy in patients with FEV_1 less than 30% or greater than 65%, and use in this population is not currently recommended.
- All alpha1-Pis are approved for 60 mg/kg once a week dosing.

Background [1,2]

- Emphysema, from any cause, is a progressive, non-curable disease, leading to decline in lung function (FEV_1), exacerbation of symptoms, decline in ability to function, and death.
- Alpha-1 antitrypsin deficiency (AATD) is a rare inherited genetic disorder, but leads to emphysema in approximately 40,000-60,000 Americans (2-3% of all emphysema patients).
- Smoking increases the risk of emphysema in patients with AATD.
- Deficient alpha-1 antitrypsin levels (A1AT) levels can lead to uninhibited lung and liver tissue breakdown from elastase and manifestations of emphysema, as well as hepatic cirrhosis.
- The ideal A1AT level with alpha1-PI repletion is uncertain. A1AT levels alone do not predict disease, as patients with very low A1AT levels can have normal lung function.
- There are four alpha1-PI products (Aralast NP, Glassia, Prolastin-C, and Zemaira) available for repletion of A1T1 levels ("augmentation therapy"), with a goal of slowing disease progression. [1,2]

Clinical Efficacy

- Alpha1-Pis replete A1AT levels, a surrogate endpoint, and the basis for their FDA approval; however, their effect on attenuation of emphysema progression with clinically meaningful efficacy endpoints (e.g., survival, quality of life) is uncertain. [3]
- Augmentation therapy with alpha1-Pis has not yet been proven to provide benefit in reversing or decreasing outflow obstruction (emphysema) associated with AATD. [4]
- There is no evidence that there is any difference in efficacy between the alpha1-PI products.
- Although there is low certainty in the evidence that alpha1-PI therapy improves health outcomes in patients with emphysema due to AATD, the products in the class appear to be similar in biologic activity.
- Despite the insufficient evidence for health outcomes with alpha1-Pis, treatment options for patients with moderate to severe emphysema are limited to symptomatic management, aside from lung transplantation. [4,5]
- There is no evidence to support the use of doses greater than 60 units/kg weekly. One small, short-term (8-week), safety and pharmacokinetic trial of higher doses of alpha1-PI (Prolastin C) in patients with AATD resulted in higher steady state levels of alpha-1 PI concentrations. However, the effect of these higher alpha-1 PI concentrations on long-term emphysema disease progression is unknown. [6]
- Treatment guidelines recommended use of augmentation therapy with alpha1-Pis for patients **WITH** airflow obstruction from AATD and FEV_1 between 30% and 65%, but do not differentiate between products. Patients should be confirmed nonsmokers or ex-smokers and plasma AAT levels less than 11 mMol/L. Patients with a heterozygous phenotype and AAT levels that exceed 11 mMol/L should not be treated with alpha1-PI augmentation therapy. [5,7]
- There is no evidence that augmentation therapy improves outcomes in patients with the MZ or other heterozygote genotypes that include a normal M gene. Guidelines state that there is neither a biologic nor evidence rationale to support treatment these individuals.[7]
- There is no evidence that augmentation therapy with alpha1-Pis are effective for treatment of AATD-related liver disease, including, hepatic cirrhosis or post liver transplant. Guidelines recommend against the use of alpha1-PIs for AATD-related liver or other AATD-related diseases.[7]

Safety

- Adverse events with alpha1-PIs are generally mild, including headache and malaise. [8]
- There is no conclusive evidence of difference in safety or immunogenicity between alpha1-PIs. [9]

Dosing and Administration [8]

- All alpha1-PIs are dosed once weekly via intravenous infusion.
- Alpha1-PI (Glassia) and Alpha-PI (Prolastin-C) are the only liquid preparations.

Codes	Number	Description
HCPCS	J0257	Glassia, Alpha 1-proteinase inhibitor, human 10 mg IV, liquid
HCPCS	J0256	Aralast NP, Prolastin-C, Zemaira, Alpha 1-proteinase inhibitor, human 10 mg IV, powder

Appendix 1. Alpha-1 Proteinase Inhibitor Product Characteristics [10-13]

Product	Aralast NP	Glassia	Prolastin-C	Zemaira
Dosage form	powder for solution	premixed solution	powder for solution	powder for solution
Concentration	1 gm/50 mL	1 gm/50 mL	1 gm/20 mL	1 gm/20 mL
Rate of infusion (mL/kg/minute)	0.08	0.2	0.08	0.08
Usual infusion time	30-40 minutes	15 minutes	15 minutes	15 minutes
Stability after mixing	3 hours	Premixed	3 hours	3 hours
Refrigeration required	No	Yes, stable for 1 month at room temperature	Yes, stable for 1 month at room temperature	No
Vial size (gm)	0.5 and 1 gm	1 gm/50 mL	1 gm	1, 4, and 5 gm

Cross References
Site of Care Review, Medication Policy Manual, Policy No. dru408

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Revision History

Revision Date	Revision Summary
6/20/2024	Added **A**lpha-1 proteinase inhibitors to site of care (SOC) program (effective 10/1/2024).
12/7/2023	No criteria changes with this annual review.
12/9/2022	Added criteria excluding patients with MZ genotype in line with guidelines. Clarified who is not recommended by guidelines for therapy in clinical efficacy. No change to intent.
10/15/2021	Updated benefit language in Administration section. Added Prolastin-C to Dosage and Administration section to show that it is also a liquid formulation.
4/22/2021	No criteria changes with this annual update
1/22/2020	Added continuation of therapy (COT) criteria (no change to intent of coverage criteria).
1/31/2019	Added diagnostic criteria requirements in line with clinical guidelines. Clarified documentation requirements.
2/16/2018	No criteria changes with this annual update.
12/16/2016	No criteria changes with this annual update.
12/11/2015	No criteria changes.
12/14/2014	New policy.

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Medication Policy Manual | **Policy No:** dru383

Topic: Vectibix, panitumumab | **Date of Origin:** May 1, 2015

Committee Approval Date: July 22, 2020 | **Next Review Date:** July 2021

Effective Date: July 1, 2020

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Panitumumab (Vectibix) is a monoclonal antibody used to treat metastatic colorectal cancer (CRC).

Policy/Criteria

Most contracts require pre-authorization approval of panitumumab (Vectibix) prior to coverage.

I. Continuation of therapy (COT): Panitumumab (Vectibix) may be considered medically necessary for COT when there is clinical documentation (including, but not limited to chart notes) confirming that criteria A. and B. below are met.

A. The patient is established on this therapy AND one of the following situations applies (criteria 1. or 2. below):

1. Prior to current health plan membership AND the medication was covered by another health plan.

Note: If the diagnosis is not listed in the coverage criteria below, written documentation of coverage must be provided, such as an approval letter or paid claim.

OR

2. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission AND there is documented clinical benefit.

AND

B. If the diagnosis is not listed in the coverage criteria below, documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria, is provided.

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. Panitumumab (Vectibix) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) confirming a diagnosis of metastatic colorectal cancer (CRC) and no RAS mutation is present (for use with KRAS and NRAS wild type tumors only).

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services does not consider panitumumab (Vectibix) to be a self-administered medication.

B. Authorization may be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

IV. Panitumumab (Vectibix) is considered investigational when used for all other conditions, including but not limited to:

A. When used concomitantly with any other targeted therapy, including, but not limited to, bevacizumab

B. Biliary tract cancer

C. Breast cancer

D. Cervical cancer

E. Esophageal adenocarcinoma

F. Gastric cancer

G. Non-small cell lung cancer (NSCLC)

H. Ovarian cancer

I. Pancreatic cancer

J. Renal cell carcinoma

K. Head and neck squamous cell carcinoma (HNSCC)

Position Statement

- Panitumumab (Vectibix), an intravenously administered monoclonal antibody that targets epidermal growth factor receptor (EGFR), has been shown to be safe and effective when used in the treatment of metastatic colorectal cancer (CRC) when no RAS mutation is present.
- The intent of this policy is to cover panitumumab (Vectibix) for the indications, regimen, and dose for which it has been shown to be safe and effective, as detailed in the coverage criteria.
- In CRC, mutations in a specific protein, the RAS protein, are associated with resistance to panitumumab (Vectibix). Therefore, panitumumab (Vectibix) therapy is not effective in CRC when RAS mutations are present (i.e. only effective in KRAS and NRAS wild-type tumors).
- Panitumumab (Vectibix) is being studied in several other types of cancers that overexpress EGFR. However, the evidence is preliminary and larger studies are needed to establish safety and efficacy of panitumumab (Vectibix) in these cancers.

Regence Pharmacy Services performs independent analyses of oncology medication evidence. NCCN clinical practice guidelines assignment of a category 2a/b recommendation does not necessarily establish medically necessity. The Regence Pharmacy Services analysis and coverage policy may differ from NCCN clinical practice guidelines.

Clinical Efficacy

COLORECTAL CANCER

- One large, randomized trial and a high-quality systematic review have evaluated the efficacy of panitumumab (Vectibix) in colorectal cancer (CRC) in different settings.
    * No difference in overall survival was observed between patients with previously untreated (treatment naïve) KRAS wild-type metastatic CRC who received panitumumab plus chemotherapy (FOLFOX) versus chemotherapy alone (FOLFOX). [1]

    * In the second-line setting and beyond, there was no difference in overall survival (OS) observed between panitumumab (Vectibix) monotherapy and best supportive care in KRAS wild-type metastatic CRC. [2]

- A small phase II comparative study evaluated add-on panitumumab (Vectibix) versus add-on bevacizumab in treatment naïve KRAS wild-type metastatic CRC. [3]
    * There was no difference in progression-free survival reported between groups.
    * There was a trend toward improved overall survival with panitumumab (Vectibix) relative to bevacizumab; however, median overall survival has not yet been reached.
- A study comparing panitumumab (Vectibix) monotherapy with cetuximab (Erbitux) monotherapy in patients with KRAS wild-type metastatic CRC who had disease progression or intolerance to several chemotherapy regimens (fluorouracil, oxaliplatin-, and irinotecan-based regimens) detected no difference in OS between the two therapies. [4]
- Further retrospective and prospective analyses of clinical trials of panitumumab (Vectibix) in metastatic CRC demonstrated improvements in overall survival in patients with wild-type NRAS when treated with panitumumab (Vectibix) plus best supportive care compared to patients treated with best supportive care alone.
- The National Comprehensive Cancer Network (NCCN) Colon Cancer and Rectal Cancer guidelines list panitumumab (Vectibix) as an option for advanced or metastatic CRC when given in combination with FOLFOX, FOLFIRI, or irinotecan when no KRAS or NRAS mutation is present. [5,6]
- There is insufficient evidence to support the use of panitumumab (Vectibix) concomitantly with any other targeted therapy, including, but not limited to, bevacizumab.

OTHER CANCERS

- Panitumumab (Vectibix) is being studied in a variety of other cancers, including, but not limited to, non-small cell lung cancer (NSCLC), head and neck squamous cell carcinoma (HNSCC), and renal cell carcinoma (RCC). [7]
    * *NSCLC:* A small (n =19) open-label, dose-escalation phase 2 trial found that panitumumab (Vectibix) in combination with standard chemotherapy was active in the treatment of advanced NSCLC. Larger, well-controlled trials are needed to establish the safety and efficacy of panitumumab (Vectibix) for NSCLC. [8]
    * *RCC:* Panitumumab (Vectibix) demonstrated minimal activity in the treatment of metastatic renal cell carcinoma in an open-label, multicenter, dose-escalating phase 2 trial (n = 88). [8]
    * *HNSCC:* Although panitumumab (Vectibix) has been extensively evaluated in HNSCC, it should not be substituted for cetuximab (Erbitux) in HNSCC.
        o When panitumumab (Vectibix) was added to cisplatin-based chemotherapy in patients with recurrent or metastatic HNSCC (SPECTRUM study), there was no improvement in overall survival (OS) over chemo-therapy alone, and grade 3 and 4 adverse effects were more frequent. [9]

- In a study comparing panitumumab (Vectibix) plus radiotherapy with cisplatin plus radiotherapy (CONCERT-2 study) in patients with unresected, locally advanced HNSCC who had received no prior therapy, local-regional control of the disease at 2 years was inferior in the panitumumab (Vectibix) treatment arm. [10]
- A second study (CONCERT-1 study) comparing (Vectibix) plus chemoradiotherapy with chemoradiotherapy alone showed similar results. [11]
- A phase 2 trial comparing docetaxel/cisplatin with or without panitumumab (Vectibix) as a first-line therapy in patients with recurrent or metastatic HNSCC demonstrated a small numerical improvement in progression-free survival (PFS) in the panitumumab (Vectibix) treatment arm; however, there was no difference in OS. [12]
- The NCCN head and neck treatment guideline does not recommend panitumumab (Vectibix) as a treatment option for HNSCC. [13]

Safety [14]

* Panitumumab (Vectibix) labeling contains a boxed warning for dermatologic toxicity.
* Other potentially serious safety concerns with panitumumab (Vectibix) include pulmonary fibrosis/interstitial lung disease, electrolyte depletion, ocular toxicity, and increased mortality with chemotherapy.

Dosing and Administration [14]

* Panitumumab (Vectibix) is given as an intravenous infusion every 14 days.

Cross References
Non-Preferred Products with Available Biosimilars/Reference Products (bevacizumab, rituximab, trastuzumab), Medication Policy Manual, Policy No. dru620
Braftovi, encorafenib, Medication Policy Manual No. dru555
Cyramza, ramucirumab, Medication Policy Manual No. dru355
Erbitux, cetuximab, Medication Policy Manual, Policy No. dru187
Keytruda, pembrolizumab, Medication Policy Manual, Policy No. dru367
Lonsurf, trifluridine/tipiracil, Medication Policy Manual, Policy No. dru434
Opdivo, nivolumab, Medication Policy Manual, Policy No. dru390
Stivarga, regorafenib, Medication Policy Manual, Policy No. dru284
Yervoy, ipilimumab, Medication Policy Manual No. dru238
Zaltrap, ziv-aflibercept, Medication Policy Manual, Policy No. dru279

Codes	Number	Description
HCPCS	J9303	Injection, panitumumab, 10 mg

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Revision History

Revision Date	Revision Summary
7/22/2020	Added continuation of therapy (COT) criteria (no change to intent of coverage criteria). Removed references to brand Avastin to account for upcoming changes to biosimilars policy (dru620).
7/24/2019	• Updated policy with standard language (no chang to policy intent). • Add use in combination with any other targeted therapy, including, but not limited to, bevacizumab to the list of Investigational uses.
11/16/2018	No criteria changes with this annual update
11/10/2017	Clarified criteria to include wild-type NRAS
8/12/2016	No criteria changes with this annual update.
1/8/2016	No criteria changes.

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Medication Policy Manual

Policy No: dru385

Topic: Complement Inhibitors

- Empaveli, pegcetacoplan
- Fabhalta, iptacopan
- Soliris, eculizumab
- Tavneos, avacopan
- Ultomiris, ravulizumab-cwvz
- Veopoz, pozelimab
- Voydeya, danicopan
- Zilbrysq, zilucoplan

Date of Origin: January 19, 2015

Committee Approval Date: June 20, 2024

Next Review Date: 2025

Effective Date: November 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Complement inhibitors are medications that bind to and inhibit the complement protein, preventing proteins from destroying red blood cells. They are used to treat specific rare blood and inflammatory disorders.

PLEASE NOTE: This policy and the coverage criteria below do **not** apply to Syfovre (pegcetacoplan intravitreal) or Izervay (avacincaptad pegol intravitreal solution).

Policy/Criteria

Most contracts require pre-authorization approval of complement inhibitors prior to coverage.

I. Continuation of therapy (COT): Complement inhibitors may be considered medically necessary for COT when criterion A, B, and C below is met.

A. One of the following (1, 2, or 3):

1. For diagnoses NOT listed in the coverage criteria below, criteria a and b must be met:

a. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

b. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

2. For diagnoses listed in the coverage criteria below, criteria a and b must be met:

a. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

b. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

3. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

AND

B. **Soliris (eculizumab) OR Ultomiris (ravulizumab-cwvz) IV only:** Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, Site of Care Review, dru408].

AND

C. "Administration, Quantity Limitations, and Authorization Period" below applies, as well as "Investigational Uses" for combination therapy.

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Complement inhibitors (as listed in *Table 1*) may be considered medically necessary when clinical documentation (including, but not limited to chart notes) that the applicable diagnosis-based criteria below are met.

Table 1:

Diagnosis: Atypical hemolytic uremic syndrome (aHUS) (a form of complement-associated thrombotic microangiopathy [TMA])	
Coverable medication(s)	**AND the following are met:**
• Soliris IV (eculizumab) • Ultomiris IV/SC (ravulizumab-cwvz)	**1.** The diagnosis has been established by or in consultation with a specialist in hematology or nephrology. **AND** **2.** Common causes of typical hemolytic uremic syndrome have been ruled out, including both of the following (criteria i and ii): **1.** Infectious causes of HUS, including Shiga toxin-related hemolytic uremic syndrome has been ruled out. **AND** **2.** Thrombotic thrombocytopenic purpura (TTP) has been ruled out [confirmed by a disintegrin and metalloprotease with thrombospondin type 1 motif, 13 (ADAMTS13) activity ≥10%]. **AND** **3.** *For Soliris (eculizumab) only*: Ultomiris (ravulizumab) has been ineffective as documented by symptom relapse or not tolerated unless there is documented medical contraindication to use. **AND** **4.** *Soliris (eculizumab) OR Ultomiris (ravulizumab-cwvz) IV only*: Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, Site of Care Review, dru408].
Diagnosis: Active severe anti-neutrophil cytoplasmic autoantibody (ANCA) associated vasculitis (granulomatosis with polyangiitis [GPA] and microscopic polyangiitis [MPA])	
Coverable medication(s)	**AND the following are met:**
• Tavneos (avacopan)	**1.** The diagnosis has been established by or in consultation with a rheumatologist**.** **AND**

	2. The patient has been screened for hepatitis B virus and severe hepatic impairment and is negative for both. **AND** **3.** The patient has an EGFR ≥15ml/min and does not require dialysis or a kidney transplant. **AND** **4.** The patient will continue to receive standard of care therapy, including but not limited to, rituximab, cyclophosphamide, glucocorticoids, azathioprine, methotrexate, or mycophenolate mofetil. **AND** **5.** The patient has previously failed induction with standard therapy (rituximab or cyclophosphamide with glucocorticoids) or has relapsed since previously achieving remission within the previous 12 months.
Diagnosis: CD55-deficient protein-losing enteropathy (CHAPLE disease)	
Coverable medication(s)	**AND the following are met:**
• Soliris IV (eculizumab) • Veopoz (pozelimab)	**1.** The diagnosis has been established by a specialist (immunologist, hematologist, gastroenterologist, or medical geneticist.) **AND** **2.** Documented confirmation of the CD55 loss of function genetic mutation. **AND** **3.** *For Veopoz (pozelimab) only:* Soliris IV (eculizumab) has been ineffective (as documented by no clinical response after 3 months of treatment), or not tolerated unless there is documented medical contraindication to use. **AND** **4.** *Soliris (eculizumab) only*: Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, Site of Care Review, dru408].

Diagnosis: Refractory myasthenia gravis (MG)	
Coverable medication(s)	**AND the following are met:**
• Soliris IV (eculizumab) • Ultomiris IV (ravulizumab-cwvz) • Zilbrysq (zilucoplan)	**1.** The diagnosis has been established by or in consultation with a neurologist who is a sub-specialist in neuromuscular disorders. **AND** **2.** A positive serologic test for anti-acetylcholine receptor (anti-aChR) antibodies. **AND** **3.** Prior to starting complement inhibitor therapy, there is documentation of a myasthenia gravis activities of daily living (MG-ADL) score of greater than or equal to 6. **AND** **4.** Both the following (criteria i and ii) have been ineffective (lack of MG symptom control or relapse as verified by a MG scoring tool), or not tolerated unless there is documented medical contraindication to use: **i.** The patient has had a thymectomy. **AND** **ii.** At least ONE neonatal Fc receptor (FcRn) antagonist [Rystiggo (rozanolixizumab), Vyvgart/Vyvgart Hytrulo (efgartigimod)]. **AND** **5.** *Soliris (eculizumab) OR Ultomiris (ravulizumab-cwvz) IV only*: Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, Site of Care Review, dru408].
Diagnosis: Neuromyelitis Optica Spectrum Disorder (NMOSD)	
Coverable medication(s)	**AND the following are met:**

• Soliris IV (eculizumab) • Ultomiris IV (ravulizumab-cwvz)	**1.** The diagnosis has been established by or in consultation with a neurologist. **AND** **2.** Documentation of a positive serologic test for aquaporin-4 immunoglobulin (AQP4-IgG) antibodies. **AND** **3.** Rituximab has been ineffective as documented by symptom relapse after completion of induction (at least one month after the first dose of rituximab) or not tolerated unless there is documented medical contraindication to use. **AND** **4.** *For Soliris (eculizumab) only*: Ultomiris (ravulizumab) and Enspryng (satralizumab) and Uplizna (inebilizumab) have been ineffective as documented by symptom relapse or not tolerated unless there is documented medical contraindication to use. **AND** **5.** Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, Site of Care Review, dru408].
Diagnosis: Paroxysmal nocturnal hemoglobinuria (PNH)	
Coverable medication(s)	**AND the following are met:**
• Empaveli (pegcetacoplan) • Fabhalta (iptacopan) • Soliris IV (eculizumab) • Ultomiris IV/SC (ravulizumab-cwvz) • Voydeya (danicopan)	**1.** The diagnosis has been confirmed by high sensitivity flow cytometry and established by or in consultation with a specialist in hematology. **AND** **2.** The complement inhibitor will be used in one of the following two settings, based on prior therapy used (i or ii): **i.** **For complement-naïve PNH** [Empaveli, (pegcetacoplan), Soliris (eculizumab), and Ultomiris IV/SC (ravulizumab-cwvz) only]: both of the following criterion (a and b) below are met: **a.** One of the following criteria (1 or 2) below are met: **1.** Transfusion-dependence prior to initiation of complement inhibitor

	treatment. ***PLEASE NOTE:*** *Transfusion-dependence is defined as at least one transfusion in the previous 24 months due to documented hemoglobin < 9 g/dL in patients with symptoms from anemia or < 7 g/dL regardless of symptoms.* **OR** **2.** A history of a major adverse vascular event from thromboembolism, including but not limited to: deep vein thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI), ischemic stroke, peripheral arterial disease (PAD), and/or Budd-Chiari syndrome. **AND** **b.** *For Soliris (eculizumab) only*: Ultomiris (ravulizumab) has been ineffective as documented by symptom relapse or not tolerated unless there is documented medical contraindication to use. **OR** **ii. <u>For complement-experienced PNH</u>** [*Empaveli (pegcetacoplan), Fabhalta (iptacopan), and Voydeya (danicopan) only]*, when breakthrough symptoms despite at least 6 months of C5 inhibitor [Soliris (eculizumab) or Ultomiris (ravulizumab)], defined as either criterion (a or b) below are met: **a.** Transfusion-dependence. ***PLEASE NOTE:*** *Transfusion-dependence is defined as at least one transfusion in the previous 6 months due to documented hemoglobin < 9 g/dL in patients with symptoms from anemia or < 7 g/dL regardless of symptoms.* **OR** **b.** A major adverse vascular event from thromboembolism, including but not limited to: deep vein thrombosis (DVT), pulmonary embolism (PE), myocardial

	infarction (MI), ischemic stroke, peripheral arterial disease (PAD), and/or Budd-Chiari syndrome. **AND** **3.** *Soliris (eculizumab) OR Ultomiris (ravulizumab-cwvz) IV only*: Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, Site of Care Review, dru408].

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Empaveli SC (pegcetacoplan), Fabhalta oral (iptacopan), Tavneos oral (avacopan), Ultomiris SC (ravulizumab-cwvz), Voydeya oral (danicopan), and Zilbrysq SC (zilucoplan) coverable only under the pharmacy benefit (as self-administered medications).

B. Regence Pharmacy Services considers Soliris IV (eculizumab), Ultomiris IV (ravulizumab-cwvz), or Veopoz IV/SC (pozelimab) coverable only under the medical benefit (as provider-administered medications).

C. When pre-authorization is approved, complement inhibitors will be covered in quantities as follows:

1. **Initial Authorization**: Up to the dose and duration, as listed below in *Table 2*:

Table 2. Initial Authorization

Indication	Authorization Limits
PNH	**Empaveli (pegcetacoplan):** Up to **48** (1080 mg) **vials** in a **24-week period**, based on SC twice weekly dosing.
	Fabhalta (iptacopan): Up to **60 (200 mg) capsules** in a **30- day period** based on twice daily oral dosing.
	Soliris (eculizumab): Up to **18** IV infusions in a **24-week period**, based on weekly dosing for five weeks, followed by maintenance dosing every 2 weeks thereafter.
	Ultomiris (ravulizumab-cwvz): **IV**: Pediatrics (<20 kg): Up to **eight** IV infusions in a **24-week period**, based on a loading dose at week 0, followed by maintenance dosing at week 2 and every 4 weeks thereafter. **IV**: Adults and Pediatrics (≥20 kg): Up to **five** IV infusions in a **24-week period**, based on a loading dose at week 0, followed by maintenance dosing at week 2 and every 8 weeks thereafter. **SC**: Adults (≥40 kg): Up to **24 doses in a 24-week period** (not to exceed 490 mg/dose), based on dose of 490 mg SC once weekly.
	Voydeya (danicopan): up to **180 (50 mg or 100 mg) tablets** in a **30-day period** based on three times daily oral dosing.

Indication	Authorization Limits
aHUS	**Soliris (eculizumab):** Pediatrics (<10 kg): Up to **10** IV infusions in a **24-week period**, based on induction dosing weekly for two weeks, followed by maintenance dosing every 3 weeks thereafter. Pediatrics (10 kg to <20 kg): Up to **14** IV infusions in a **24-week period**, based on induction dosing weekly for two weeks, followed by maintenance dosing every 2 weeks thereafter. Pediatrics (20 kg to <40 kg): Up to **16** IV infusions in a **24-week period**, based on induction dosing weekly for three weeks, followed by maintenance dosing every 2 weeks thereafter. Adults and Pediatrics (≥40 kg): Up to **18** IV infusions in a **24-week period**, based on induction dosing weekly for five weeks, followed by maintenance dosing every 2 weeks thereafter.
	Ultomiris (ravulizumab-cwvz): **IV**: Pediatrics (<20 kg): Up to **eight** IV infusions in a **24- week period**, based on a loading dose at week 0, followed by maintenance dosing at week 2 and every 4 weeks thereafter. **IV**: Adults and Pediatrics (≥20 kg): Up to **five** IV infusions in a **24-week period**, based on a loading dose at week 0, followed by maintenance dosing at week 2 and every 8 weeks thereafter. **SC**: Adults (≥40 kg): Up to **24 doses in a 24-week period** (not to exceed 490 mg/dose), based on dose of 490 mg SC once weekly.
MG	**Soliris (eculizumab):** Up to **18** IV infusions in a **24-week period**, based on induction dosing weekly for five weeks, followed by maintenance dosing every 2 weeks thereafter.
	Ultomiris (ravulizumab-cwvz): IV: Up to **five** IV infusions in a **24- week period**, based on a loading dose at week 0, followed by maintenance dosing at week 2 and every 8 weeks thereafter.
	Zilbrysq (zilucoplan): Up to **one syringe per day for 24 weeks**, based on a weight-based dose <56kg=16.6mg; 56kg to <77kg=23 mg; or ≥77kg=32.4mg SC daily.
NMOSD	**Soliris (eculizumab):** Up to **fifteen** IV infusions in a **24-week period**, based on induction dosing weekly for five weeks, followed by maintenance dosing every 2 weeks thereafter.
	Ultomiris (ravulizumab-cwvz): Adults (≥40 kg): **IV**: Up to **five** IV infusions in a **24- week period**, based on a loading dose at week 0, followed by maintenance dosing at week 2 and every 8 weeks thereafter.
CHAPLE	**Soliris (eculizumab):** Pediatrics (<10 kg): Up to **nine** IV infusions in a **24-week period**, based on induction dosing weekly for two weeks, followed by maintenance dosing every 3 weeks thereafter. Pediatrics (10 kg to <40 kg): Up to **thirteen** IV infusions in a **24-week period**, based on induction dosing weekly for up to 3 weeks, followed by maintenance dosing every 2 weeks thereafter. Adults and Pediatrics (≥40 kg): Up to **fourteen** IV infusions in a **24-week period**, based on induction dosing weekly for five weeks, followed by maintenance dosing every 2 weeks thereafter.
	Veopoz (pozelimab): Up to **24 doses in** a **24-week period,** based on single one-time IV loading dose infusion on day 1 followed by weekly SC injections every week thereafter
ANCA-AV	**Tavneos (avacopan):** Up to 3 oral tablets twice daily (not to exceed 60mg per day) for 6 months.

2. **Continued Authorization:** Up the dose and duration listed below in *Table 3*:

Table 3. Continued Authorization

Indication	Soliris (eculizumab)
PNH	**Fabhalta (iptacopan):** Up to **60 (200 mg) capsules** in a **30-day** period based on twice daily oral dosing.
	Empaveli (pegcetacoplan): PNH (stable): Up to **104** (1080 mg) **vials** in a **52-week period,** based on SC twice weekly dosing. **PNH with breakthrough hemolysis** [LDH > 2x ULN, on twice weekly Empaveli: Up to **ten** (1080 mg) vials per 30 days over a **24-week period.**
	Soliris (eculizumab): **PNH (stable)**: Up to **26** IV infusions in a **52-week period**, based on maintenance dosing every **2 weeks**. **PNH with breakthrough hemolysis on every 2-week Soliris:** • Up to **31** IV infusions in a **52-week period**, based on a max dose of 900 mg every **12 days**
	Ultomiris (ravulizumab-cwvz): IV: Up to **seven** infusions in a **52-week period**, based on maintenance dosing every 8 weeks. **SC:** Up to **104 doses in a 52-week period** (not to exceed 490 mg/dose), based on dose of 490 mg SC once weekly.
	Voydeya (danicopan): up to **180 (50 mg or 100 mg) tablets** in a **30-day period** based on three times daily oral dosing.
aHUS	**Soliris (eculizumab):** Pediatric Patients (<10 kg): Up to **18** IV infusions in a **52-week period**, based on maintenance dosing every **3 weeks**. Adults and Pediatrics (≥10 kg): Up to **26** IV infusions in a **52-week period**, based on maintenance dosing every **2 weeks**.
	Ultomiris (ravulizumab-cwvz): IV: Pediatric Patients (<20 kg): Up to **13** IV infusions in a **52-week period**, based on maintenance dosing every **4 weeks**. **IV**: Adults and Pediatrics (≥20 kg): Up to **seven** IV infusions in a **52-week period**, based on maintenance every **8 weeks**. **SC**: Up to **104 doses in a 52-week period** (not to exceed 490 mg/dose), based on dose of 490 mg SC once weekly.
MG	**Soliris (eculizumab):** Up to **26** IV infusions in a **52-week period**, based on maintenance dosing every **2 weeks**.
	Ultomiris (ravulizumab-cwvz): IV: Up to **7** IV infusions in a **52-week period**, based on maintenance dosing every 8 weeks.
	Zilbrysq (zilucoplan): Up to one syringe per day for 52 weeks, based on a weight-based dose of <56kg=16.6mg; 56kg to <77kg=23 mg; or ≥77kg=32.4mg SC daily.

Indication	Soliris (eculizumab)
NMOSD	**Soliris (eculizumab):** Up to **26** IV infusions in a **52-week period**, based on maintenance dosing every **2 weeks**.
	Ultomiris (ravulizumab-cwvz): IV: Up to **7** IV infusions in a **52-week period**, based on maintenance every **8 weeks**.
CHAPLE	**Soliris (eculizumab):** Pediatric Patients (<10 kg): Up to **eighteen** IV infusions in a **52-week period**, based on maintenance dosing every **3 weeks**. Adults and Pediatrics (≥10 kg): Up to **26** IV infusions in a **52-week period**, based on maintenance dosing every **2 weeks**.
	Veopoz (pozelimab): Up to **52 SC injections in a 52- week period** based on weekly SC dosing
ANCA-AV	**Tavneos (avacopan):** Up to 3 tablets orally twice daily (not to exceed 60mg per day) for 12 months.

3. **Supplemental dosing** may be given according to label, as follows:

a. Soliris (eculizumab): after plasma exchange/plasmapheresis (PLEX) or fresh frozen plasma (FFP) infusion.

b. Ultomiris (ravulizumab): after plasma exchange/plasmapheresis (PLEX) or intravenous immunoglobulin (IVIG).

4. Use of doses in excess of those listed above (in *Tables 1* and *2*) are considered not medically necessary.

D. Authorization **shall** be reviewed as follows (per the authorization time frames, as specified in *Tables 1* and *2*) to confirm that current medical necessity criteria are met and that the medication is effective.

1. **For all indications**: Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met and that the medication is providing clinical benefit, including disease stability or improvement must be provided, relative to baseline symptoms.

2. **In addition, the following diagnostic-specific** clinical documentation must be provided:

a. **For MG**: A standard disease scoring tool must be included, such as the total myasthenia gravis activities of daily living (MG-ADL) score, total quantitative myasthenia gravis (QMG) score, and/or myasthenia gravis composite (MGC) scale.

b. **For NMOSD:** There must be a reduction of clinical relapse OR provider attestation has been received that patient is continuing to have clinical benefit (stability or improvement) and continued therapy is medically necessary.

c. **For CHAPLE:** There must be a reduction in baseline symptoms such as visceral and peripheral edema, diarrhea, and abdominal pain, AND/OR a reduction in the need for supportive care including infusions of albumin and/or immunoglobulin, corticosteroid use, and hospitalizations.

IV. Complement inhibitors (as listed in *Tables 1* and *2*) are considered investigational when used for all other conditions, including but not limited to:

A. Amyotrophic lateral sclerosis (ALS).

B. Delayed hemolytic transfusion reaction in sickle cell disease.

C. Deposit disease/C3 glomerulonephritis.

D. Hemolytic cold agglutinin disease.

E. Ocular myasthenia gravis.

F. Myasthenia gravis with MUSK antibodies or antibodies other than anti-ACh-R.

G. Non-exudative (dry) macular degeneration.

H. Preeclampsia with hemolysis, elevated liver enzymes and low platelets (HELLP) syndrome.

I. Prevention of delayed graft rejection.

J. Shiga toxin E. coli-related hemolytic uremic syndrome (STEC-HUS) Systemic lupus erythematosus.

K. Thrombotic thrombocytopenic purpura (TTP).

L. For NMOSD: Use of multiple targeted therapies for NMOSD, including but not limited to complement inhibitors (such as Ultomiris [ravulizumab-cwvz], Soliris [eculizumab], anti-CD20 therapy [rituximab product], anti-CD19 therapy [Uplizna (inebilizumab)], or anti-IL6 therapy [Actemra (tocilizumab)], Enspryng (satralizumab)].

M. For PNH: Combination use of the following complement inhibitors (Empaveli [pegcetacoplan], Fabhalta [iptacopan], Soliris [eculizumab], Ultomiris [ravulizumab-cwvz]).

N. Use of Fabhalta (iptacopan) in C5-inhibitor naïve PNH.

O. For gMG: Use in combination with other targeted therapies for MG, such as FcRn antagonists (Vyvgart [efgartigimod] or Rystiggo [rozanolixizumab]) or IVIG maintenance therapy.

P. Eosinophilic granulomatosis with polyangiitis (EPGA, formerly known as Churg-Strauss Syndrome).

Q. Hidradenitis Suppurativa.

R. Use of Tavneos (avacopan) for aHUS.

S. Use of Tavneos (avacopan) for non-severe ANCA- associated vasculitis.

T. Use of Veopoz (pozelimab) for aHUS, MG, NMOSD, or PNH.

Position Statement

- Complement inhibitors (as listed in *Table 1*) are monoclonal antibodies that bind to complement proteins and inhibit activation of the complement pathway.
    * Empaveli (pegcetacoplan), Fabhalta (iptacopan), and Voydeya (danicopan) are proximal complement inhibitors.
    * Soliris (eculizumab), Ultomiris (ravulizumab-cwvz), Veopoz (pozelimab), and Zilbrysq (zilucoplan) are terminal complement inhibitors, also referred to as complement 5 inhibitors ("C5 inhibitors").
    * Tavneos (avacopan) is an orally administered complement 5a (C5a) receptor antagonist that inhibits the C5a-mediated neutrophil activation and migration pathway.
- The intent of the policy is to allow for coverage of complement inhibitors for the specific diagnoses for which they have been studied (as outlined in the coverage criteria), when managed by a specialist, limit to more severe disease and encourage the use of lower cost therapies (when appropriate), and limit coverage to doses studied and shown to be safe and effective in clinical trials. For diagnoses with multiple targeted treatment options for refractory disease, including compliment inhibitors, higher cost targeted treatment options are coverable only when lower cost targeted treatments are not an option.
    * Where there is lack of proven additional benefit and/or lack of demonstrated health outcomes relative to alternative therapies, use of complement inhibitors alone or in combination with other therapies is not coverable ("not medically necessary" or "investigational").
    * It is important to note that a medication being FDA approved for a specific indication does not, in itself, make the treatment medically reasonable and necessary.
- Ultomiris (ravulizumab-cwvz) is a complement inhibitor that is a derivative of Soliris (eculizumab) with a more convenient, extended dosing regimen. It is coverable only for the indications for which it has been studied and the dose is known, as detailed in the coverage criteria.
- Tavneos (avacopan) is FDA approved for adjunctive use in severe active anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis, including granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) in combination with standard therapy. However, the health plan considers use in newly diagnosed patients to be non-coverable as this regimen has not adequately been demonstrated to provide any superior benefit versus the lower-cost standard of care treatment options.
- Veopoz (pozelimab) approved only for use in CD55-deficient protein-losing enteropathy, also known as CHAPLE disease is only coverable when the lower cost alternative Soliris (eculizumab) has been ineffective or not tolerated.

Paroxysmal nocturnal hemoglobinuria (PNH) summary

- PNH is a rare and life-threatening blood disorder, characterized by a reduced (type II) or deficient (type III) glycosylphosphatidylinositol (GPI)-linked proteins from the surface of red blood cells. The GPI-linked protein CD59 blocks the formation of the terminal complement

complex, preventing cell lysis. In the absence of CD59, red blood cells are susceptible to complement-mediated lysis leading to anemia, hemoglobinuria, and other complications. [1 2]

- There are few treatment options for patients with PNH.
  * Active monitoring of the patient is appropriate for those with mild disease; however, most will require palliative therapy. Treatment is not standard, as the approach to treatment is specific to the manifestations of each patient's disease. Blood transfusions, anticoagulation, and supplementation with folic acid or iron may be required. [3]
  * Allogeneic hematopoietic cell transplantation (HCT) is the only curative therapy for PNH and is typically reserved for only the most severe patients due to barriers such as high rates of morbidity and mortality, and lack of suitable donors. [4]
  * FDA-approved therapies for PNH include terminal complement inhibitors [C5 inhibitors Soliris (eculizumab) and Ultomiris (ravulizumab-cwvz)], and proximal inhibitors [Empaveli (pegcetacoplan), Fabhalta (iptacopan), Voydeya (danicopan)]. These treatments are not curative, so patients are treated indefinitely. [3]
  * C5 inhibitors, including Ultomiris (ravulizumab and Soliris (eculizumab), have become the standard of care for PNH, as clinical experience has shown their utility in reducing symptoms and thrombosis. More recently, proximal inhibitor Empaveli (pegcetacoplan) has also been shown to be safe and effective as an alternative to C5 inhibitor use in complement-naïve PNH.
  * Some patients continue to have breakthrough symptoms despite treatment with standard doses of C5 inhibitors [Ultomiris (ravulizumab and Soliris (eculizumab)]. Proximal inhibitors [Empaveli (pegcetacoplan), Fabhalta (iptacopan), or Voydeya (danicopan)] may be coverable when standard of care C5 inhibitors are ineffective or not a treatment option for complement-experienced PNH.
    - In the pivotal trials of Fabhalta (iptacopan) and Voydeya (danicopan) for treatment-experienced PNH, patients were established on at least 6 months of C5-inhibitor therapy and having breakthrough symptoms. Most patients had at least one transfusion in the 6 months prior to the study. [5-8]
    - Empaveli (pegcetacoplan) has also been studied in complement-naive PNH, as well as complement-experienced PNH.
- There is no scientific basis to prefer one FDA-approved C5 inhibitor over another (by mechanism of action); given similar efficacy and safety, most contracts consider more costly products not medically necessary. Specifically, at this time, Ultomiris (ravulizumab) is the lower cost C5 inhibitor for PNH. Therefore, higher cost C5 inhibitor, Soliris (eculizumab), is coverable only when the overall lower cost option, Ultomiris (ravulizumab), is not a treatment option.
- According to the American Society of Hematology (ASH) guidelines, complement inhibitor therapy should be considered in patients with significant symptoms from

hemolysis that are not adequately managed with transfusion. Additionally, most patients included in clinical trials received transfusions prior to enrollment=.[9]

- Thrombosis is a common manifestation of PNH and the leading cause of mortality in this population. Due to the severity of the condition, lack of treatment options, and long-term data that suggests efficacy in preventing thrombotic events, complement inhibitor therapy is appropriate for secondary prevention in patients who have experienced a cardiovascular event due to thrombosis, regardless of transfusion history. For patients with underlying bone marrow failure from aplastic anemia, therapy should target the underlying bone marrow failure, as these patients are less likely to experience benefit from complement inhibitor therapy. [3]
- Treatment with complement inhibitors (C5 inhibitors and proximal inhibitors) may be considered effective if there is a decrease in the number of transfusions or disabling symptoms, stabilization of hemoglobin levels, a reduction in thrombotic events, and/or an improvement in quality of life.
- Complement Inhibitors (*as listed in Table 1*) may be covered for PNH at the doses proven to be safe and effective in clinical trials.
- *Higher dosing for refractory PNH*: For breakthrough hemolysis with PNH, Soliris (eculizumab) can be dosed more frequently (at 900 mg every 12 days). However, higher dosing of Soliris (eculizumab) (1200 mg every 14 days) is considered 'not medically necessary," as is more costly but not proven to be safer or more effective than more frequent dosing for breakthrough PNH. In addition, there are several complement inhibitor options now available for breakthrough PNH, including Empaveli (pegcetacoplan), Fabhalta (iptacopan), and Voydeya (danicopan). For breakthrough hemolysis with PNH when LDH exceed two times the upper limit of normal (ULN), Empaveli (pegcetacoplan) can be dosed at 1080 mg every three days.

Atypical hemolytic uremic syndrome (aHUS) summary

- Hemolytic uremic syndrome (HUS) is a condition caused by the premature destruction of red blood cells and is characterized by microangiopathic hemolytic anemia, thrombocytopenia, and acute kidney injury (>95% of patients). [11] Acute presentation may also include neurological findings (including seizures), gastrointestinal symptoms, and cardiovascular involvement (including hypertensive emergency and acute coronary events. Chronic kidney disease (CKD) is the most common long-term sequelae, including the need for dialysis. [12]
    * The most common cause of HUS is infection, with most cases in the United States being associated with Shiga toxin-producing E. coli. There are no randomized, controlled trials that show complement inhibitors are safe or effective in the treatment of infectious-HUS.
    * Non-infectious HUS, known as atypical hemolytic uremic syndrome (aHUS), typically results from complement abnormalities. However, aHUS is a diagnosis of EXCLUSION, meaning the diagnosis of aHUS is made by excluding other primary thrombotic microangiopathy (TMA) syndromes, such as TTP or infectious HUS.

    * As a complement-related TMA, aHUS is also referred to as complement-related HUS. [4 11 13]

- Thrombotic thrombocytopenic purpura (TTP) is group of syndromes in which patients usually present with thrombocytopenia and microangiopathic hemolytic anemia. Despite similarities in clinical features, the underlying mechanisms of aHUS and TTP differ, altering the manner in which patients respond to different therapies.
- TTP results from mutations in the gene encoding a disintegrin and metalloprotease with thrombospondin type 1 motif, 13 (ADAMTS13). Patients who are severely ADAMTS13 deficient, defined as ADAMTS13 activity <10%, have a confirmed diagnosis of TTP and may not respond to complement-inhibitor therapy.
    * There are no randomized, controlled trials that show complement inhibitors are safe or effective in the treatment of TTP. [13 14]
- Soliris (eculizumab) and Ultomiris (ravulizumab-cwvz) are FDA-approved for complement-medicated HUS (aHUS). There are no objective biomarkers to confirm a diagnosis of aHUS; however, TTP-HUS can be ruled out if severe ADAMTS13 deficiency is not present (ADAMTS13 activity ≥ 10%). As complement inhibitors, Soliris (eculizumab) and Ultomiris (ravulizumab-cwvz) target the underlying mechanism behind aHUS, binding to the complement protein C5 and prevent the formation of proinflammatory molecules. [15] However, complement testing is not universally used, as normal complement levels do not exclude a diagnosis of aHUS. [13]
- Prior to the availability of complement inhibitors, the treatment of choice for aHUS was plasma exchange/plasmapheresis (PLEX) or transfusion plus supportive care. Patients undergoing plasma exchanges are prone to complications including fluid-imbalance, catheter-related complications, and anaphylactic reactions. While most patients respond to plasmapheresis, patients remain at risk for chronic kidney injury. [15 16]
- Evidence of efficacy of certain complement inhibitors primarily comes from positive open-label, single arm trials, retrospective reviews, and case studies.
- Despite a lack of high-quality evidence, complement inhibitors are an important treatment option for patients with aHUS. [17] However, there are still many unknowns about complement inhibitors including evidence of efficacy for meaningful clinical outcomes, such as mortality, comparative efficacy with plasmapheresis, long term safety, and validated strategies for starting and stopping therapy.
- Treatment with certain complement inhibitors may be considered effective if treatment results in a decrease in the signs of thrombotic microangiopathy (TMA), indicated by normalization of platelet counts and lactate dehydrogenase (LDH) levels.
- There is no evidence that Soliris (eculizumab) is more effective than other compliment inhibitors (targeted aHUS product), Ultomiris (ravulizumab). Among the FDA-approved agents for refractory aHUS, Ultomiris (ravulizumab) is a lower cost option with lower administration burden. There is no scientific basis to prefer one FDA-approved targeted aHUS product over another; given similar efficacy and safety, most contracts consider more costly products not medically necessary.
- Currently there is insufficient evidence to establish the safety and efficacy of Tavneos (avacopan), an oral complement antagonist, for aHUS.

Refractory myasthenia gravis (MG) summary

- Myasthenia gravis (MG) is a rare autoimmune disease arising from T cell-dependent immunologic attack of AChR, muscle-specific tyrosine kinase (MuSK), and/or other receptors found on the postsynaptic neuromuscular junction, resulting in striated muscle weakness.
- MG presents with painless, fluctuating, fatigable weakness of specific muscle groups. Initially, patients most frequently present with ocular MG of the eyelids and extraocular muscles, presenting with asymmetric ptosis and diplopia. As weakness extends beyond ocular muscles, the disease progresses into generalized MG (gMG).
- Approximately 10-15% of all MG cases consist of refractory gMG that presents with severe debilitating muscle weakness despite substantial use of long-term corticosteroids or multiple steroid-sparing immunosuppressive agents, resulting in substantial negative effects on activities of daily living and quality of life.
- Complement inhibitors, Soliris (eculizumab),Ultomiris (ravulizumab-cwvz) and Zilbrysq (zilucoplan), provide newer treatment options for refractory gMG. While the clinical data is promising, there are several limitations in the body of evidence. Use should be limited to patients who have failed other options, as detailed in the coverage criteria.
- Standard therapies recommended by treatment guidelines for management of MG include acetylcholinesterase (ACh) inhibitors (pyridostigmine), corticosteroids, various DMARDs for immunosuppressant therapy (IST), intravenous immunoglobulin (IVIG), plasmapheresis/plasma exchange (PLEX), and thymectomy. [18-23]
    * Acetylcholinesterase inhibitors are used for temporary symptomatic relief of MG symptoms, by slowing the breakdown of acetylcholine at the neuromuscular junction. However, their use is limited as an adjunct therapy to immunotherapy in those with residual or refractory MG or for treatment of ocular and mild gMG in those who cannot receive immune suppression. [20]
    * Corticosteroids are the most widely used immune modulator for MG. Corticosteroids are effective in ocular MG and in patients with gMG with unsatisfactory responses to acetylcholinesterase inhibitors; however, they are associated with significant dose-dependent adverse events and should not be used for extended durations. [21]
    * Azathioprine, cyclosporine, and mycophenolate mofetil are standard on-steroid immunosuppressant therapy (IST) and act as steroid-sparing agents. Other options include cyclophosphamide, methotrexate, and tacrolimus. [18 19 22]
        - Onset of effect is slow (up to 9-12 months). Once goals are met, steroids may be slowly tapered; however, many patients require long-term low-dose steroids for symptom control.
        - Guidelines recommend dose adjustments no more frequently than every 3 to 6 months.
        - Once treatment effective is achieved and doses are maintained for six months to two years of therapy, IST doses should be tapered to the lowest effect dose.

* Plasma exchange/plasmapheresis (PLEX) and IVIG provides short-term symptomatic relief during exacerbations for surgical preparation or in patients with septicemia through downregulating autoantibodies and/or inducing anti-idiopathic antibodies. However, IVIG may be a maintenance treatment option for patients intolerant to or not responding to an adequate course of non-steroid IST. [23]
* Patients with thymoma should undergo thymectomy. In non-thymomatous patients, thymectomy is a treatment option to minimize need for immunotherapy (either avoid, dose minimize, or use for refractory MG symptoms). However, thymectomy may not be medically possible in unstable MG patients. [18 19]
* There is no evidence that complement inhibitors are more effective than other targeted MG products such as neonatal Fc receptor (FcRn) antagonists Vyvgart (efgartigimod) or Rystiggo (rozanolixizumab). Among the FDA-approved agents for deeply refractory gMG, FcRn antagonists are lower cost options. Among the complement inhibitors, Ultomiris (ravulizumab) and Zilbrysq (zilucoplan) may represent lower cost options with lower administration burden versus Soliris (eculizumab). There is no scientific basis to prefer one FDA-approved targeted MG product over another; given similar efficacy and safety, most contracts consider more costly products not medically necessary.

- MG-ADL is a scoring tool used in clinical practice, along with MG composite score, for monitoring progression of MG and response to therapies. [24]
- Complement inhibitors have not been studied and shown to be safe or effective in patients with other antibodies, including MuSK antibodies, antibodies to the agrin receptor low-density lipoprotein receptor–related protein 4 (LRP4), or any other antibodies. In addition, they have not been studied in patients with ocular MG (without generalized MG symptoms) or those in myasthenic crisis (MGFA Class V).
- Complement inhibitors have not been studied when used in combination with one another, with chronic maintenance IVIG, or with FcRn antagonists. In clinical trials, patients were transitioned off chronic maintenance IVIG prior to initiating complement inhibitors.
- Soliris (eculizumab), Ultomiris (ravulizumab-cwvz), and Zilbrysq (zilucoplan)may be covered for refractory MG at the doses proven to be safe and effective in clinical trials, as detailed in the coverage criteria.

Neuromyelitis optica spectrum disorder (NMOSD) summary [25-28]

- NMOSD, also known as Devic disease or neuromyelitis optica (NMO), is a chronic demyelinating disease of the central nervous system dominated by inflammation of the optic nerve and spinal cord and may often be misdiagnosed as multiple sclerosis (MS).
- Stepwise deterioration due to disease relapse/attack causes an accumulation of disability. Hallmark features of NMOSD include acute nerve inflammation that led to severe visual loss, limb weakness, sensory loss, pain, paralysis, bladder dysfunction, and intractable nausea/vomiting and hiccups.
- Patients with NMOSD are treated for acute episodes/ relapse with steroids. Plasma exchange (PLEX) is used acutely for incomplete response to steroids.

- Immunosuppressive therapy (IST; corticosteroids, azathioprine, mycophenolate mofetil, or rituximab) is therapy to reduce the frequency of relapse (maintenance therapy).
- Not all patients with NMOSD test positive for AQP4-IgG. However, all patients in clinical trials of Soliris (eculizumab) and Ultomiris (ravulizumab-cwvz) for NMOSD were AQP4-IgG positive. Therefore, the safety and efficacy of Soliris (eculizumab) and Ultomiris (ravulizumab-cwvz) in AQP4-IgG negative patients is unknown.
- Neither Soliris (eculizumab) nor Ultomiris (ravulizumab-cwvz) have not been directly compared to any other IST for NMOSD. However, use of rituximab for NMOSD is supported by clinical evidence for reducing relapse rate [including a single randomized controlled trial (RCT)] [29] is recommended by guidelines, and has years of experience in clinical practice. [25 28 30-35] Therefore Soliris (eculizumab) and Ultomiris (ravulizumab-cwvz) for NMOSD is coverable only when rituximab is ineffective or not a treatment option.
- There is no evidence that Soliris (eculizumab) is more effective than other targeted treatments for refractory NMOSD, Ultomiris (ravulizumab-cwvz), Enspryng (satralizumab) and Uplizna (inebilizumab). Among the FDA-approved targeted agents for refractory NMOSD, Ultomiris (ravulizumab-cwvz), Enspryng (satralizumab) and Uplizna (inebilizumab) are lower cost options with lower administration burden. There is no scientific basis to prefer one FDA-approved targeted NMOSD product over another; given similar efficacy and safety, most contracts consider more costly products not medically necessary.
- The evidence for Soliris (eculizumab) and Ultomiris (ravulizumab-cwvz) in NMOSD is limited to a single phase 3 trials. Although these drugs reduced the frequency of NMOSD relapse, their effect on quality life (QoL) and disability are unknown.

  The safety and efficacy combination targeted therapies for NMOSD, such as rituximab, Soliris (eculizumab), Ultomiris (ravulizumab-cwvz), Enspryng (satralizumab) and Uplizna (inebilizumab), have not be studied and have not been established.

CD55-defiecent protein-losing enteropathy (CHAPLE disease)[36]

- CHAPLE disease is a recently discovered, ultra-rare, recessive disorder, caused by mutations in the CD55 gene, leading to an overactivation of the complement system, resulting in intestinal protein loss (albumin and immunoglobulins) due to damage in blood and lymph vessels along the digestive tract.
- The spectrum of severity for CHAPLE disease is not fully characterized, however it typically presents early in childhood, causing high rates of morbidity that manifest as peripheral and visceral edema (due to severe hypoalbuminemia), diarrhea, abdominal pain, hypogammaglobulinemia, malabsorption, malnutrition, infections, and impaired growth, with severe and fatal vascular occlusions being the leading cause of mortality.
- Diagnosis of CHAPLE disease is based on clinical signs and symptoms, with confirmation via positive genetic test for CD55 loss of function mutation.
- Published data on CHAPLE disease treatment is limited due to its rarity and newness. Currently there are no consensus guidelines for CHAPLE treatment, as the only guidance has been limited to case reports and small natural history studies.

- Most treatment focuses on addressing patients' symptoms with supportive care including corticosteroids, IV albumin and immunoglobulin (IVIG/SCIG), nutrition supplementation, and anticoagulation to prevent thrombosis.
- Soliris (eculizumab) has shown efficacy in CHAPLE disease in a small observational trial for which all patients reported normalization of serum albumin and improvement in symptoms. Treatment with off label Soliris (eculizumab) has since become the standard of care for patients with CHAPLE disease.
- Veopoz (pozelimab) recently received FDA approval-based efficacy results from a small single arm trial in patients with confirmed CHAPLE disease.
- Currently, there is insufficient evidence to establish therapy with Veopoz (pozelimab) is more effective or safer than the lower-cost alternative Soliris (eculizumab), which has a much more robust real world safety profile in patients with confirmed CHAPLE disease. Therefore, the use of Veopoz (pozelimab) for patients with confirmed CHAPLE disease is coverable only in patients who have had an insufficient response or intolerance to Soliris (eculizumab).
- The safety and efficacy of combining targeted therapies for CHAPLE disease, such as Soliris (eculizumab) and Veopoz (pozelimab), has not be studied; therefore, use in combination is considered investigational.

Antineutrophil cytoplasmic antibody-associated vasculitis (ANCA-AV) (MPA or GPA) [37-41]

- ANCA-AV is a rare multisystem autoimmune disease caused by inflammation and necrosis of the small and medium arteries. ANCA-AV includes microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA, also known as Wegener's granulomatosis), and eosinophilic granulomatosis with polyangiitis (EPGA, formerly known as Churg-Strauss syndrome). However, EPGA is clinically and pathologically different from GPA and MPA, and patients with EGPA were excluded from clinical trials. Therefore, the safety and efficacy of Tavneos (avacopan) in EGPA is unknown and its use for EGPA is considered investigational.
- ANCA-AV patients usually present with nonspecific symptoms (fever, malaise, myalgias, and arthralgias) and are commonly misdiagnosed, so testing for ANCA antibody is key and tissue biopsy is confirmatory.
- The 2021 American College of Rheumatology (ACR) ANCA-AV guidelines recommend treatment based on severity of disease and organ involvement, with the goals of inducing remission and maintaining remission, as follows:
    * Non-severe active disease (<u>without</u> organ involvement or non-life-threatening):
        - First-line options for induction of remission as well as maintenance of remission include methotrexate or azathioprine in combination with glucocorticoids. Mycophenolate mofetil in combination with glucocorticoids is a second-line option if methotrexate or azathioprine is contraindicated or not tolerated.
    * Severe active disease (with organ involvement or life-threatening manifestations):

        - First-line treatment for induction of remission is rituximab in combination with low dose glucocorticoids. Cyclophosphamide (IV or oral) in combo with low dose glucocorticoids is another option for induction if previous treatment with rituximab has failed.
        - Once remission has been induced, rituximab is used as first-line treatment for the maintenance of remission. Use of oral immunosuppressants such as methotrexate, azathioprine, and mycophenolate mofetil are used as maintenance options if rituximab is not tolerated or contraindicated.
    * Tavneos (avacopan) is not included in the guidelines, which were released prior to FDA approval of Tavneos (avacopan).
- Tavneos (avacopan) received FDA approval based on a single trial as adjunctive therapy for severe ANCA-AV (MPA or GPA), in combination with standard therapy, including corticosteroids.
- Currently there is insufficient evidence to establish add-on therapy with Tavneos (avacopan) is more effective than the lower cost standard of care immunosuppressant treatment options for patients with severe active ANCA-associated vasculitis. Therefore, the use of Tavneos (avacopan) for patients diagnosed with severe ANCA-associated vasculitis will only be covered as add on therapy to the standard of care in patients who have previous failed induction therapy with standard of care options (rituximab or cyclophosphamide with glucocorticoids) or who have relapsed since previously achieving remission in the past 12 months.

Clinical Efficacy

Paroxysmal nocturnal hemoglobinuria (PNH)

- The evidence for C5 inhibitors in PNH is based on phase 3 trials showing complement inhibitors stabilize hemoglobin and reduces the need for transfusions for patients with PNH compared to placebo or standard of care. [2] Overall survival has not been evaluated in controlled, clinical trials for complement inhibitors. However, thrombosis, the main cause of permanent disability and death in PNH, is largely mitigated by existing C5 inhibitor therapies based on clinical experience.
- *Soliris (eculizumab):*
    * The TRIUMPH study is a 26 week, double-blind, randomized, placebo-controlled, multicenter trial that evaluates the efficacy and safety of Soliris (eculizumab) in PNH in 87 patients who had at least 4 transfusions during the previous 12 months.
        - At the end of the treatment period, 49% of patients treated with Soliris (eculizumab) had stabilized hemoglobin in the absence of transfusions, which was not accomplished by any patients receiving placebo ($p<0.001$).
        - Transfusion independence was achieved in 51% of patients in the Soliris (eculizumab) group and was not achieved by any patients receiving placebo ($p<0.001$).

    * In a long-term study, up to three years, patients in the analysis experienced a sustained reduction in hemolysis, measured by lactate dehydrogenase levels, and a reduction in thromboembolic events. [43]
    * Expert consensus indicates that Soliris (eculizumab) decreases hemolysis, the resultant symptoms, thrombosis, and transfusion requirements. Soliris (eculizumab) should be considered in patients with significant symptoms from hemolysis that are not adequately managed with transfusion (Grade 1A recommendation). [9]

- *Ultomiris (ravulizumab-cwvz):* The evidence for Ultomiris (ravulizumab-cwvz) is based on two trials that compared it to Soliris (eculizumab). The trials demonstrated that Ultomiris (ravulizumab-cwvz) is not worse than Soliris (eculizumab) for the treatment of PNH. [11 44-46]
    * Both trials demonstrated Ultomiris (ravulizumab-cwvz) was noninferior to Soliris (eculizumab) for measurements of hemolysis and transfusion avoidance.
    * Ultomiris (ravulizumab-cwvz) carries the same safety concerns as Soliris (eculizumab) including a REMS program and safety warning about meningitis.
    * There are ongoing clinical trials for Ultomiris (ravulizumab-cwvz) in conditions that have evidence for efficacy for Soliris (eculizumab).
- *Empaveli (pegcetacoplan):* The evidence for pegcetacoplan in PNH is primarily based on one randomized control trial (PEGASUS) in patients who were established on eculizumab and one interim phase 3 trial (PRINCE) in patients who were not on complement inhibitors at baseline.
    * The PEGASUS [47] study was a phase 3, randomized, open-label, 16-week active-control trial in 80 adults with PNH whose hemoglobin levels remained low despite treatment with eculizumab; at baseline, patients had over 6 transfusions in the 12 months prior to the study.
        - Patients in the pegcetacoplan arm demonstrated a superiority in change in hemoglobin level versus eculizumab from baseline to week 16 and noninferiority for transfusion avoidance. The benefits were sustained during the 32-week open label period. Two out of 41 patients in the pegcetacoplan group required dose escalation to 1,080 mg every 3 days.
    * The PRINCE study was a randomized, open-label, 26-week, controlled phase 3 trial in 53 adults with PNH who were not on complement inhibitors at baseline. The trial that compared pegcetacoplan with standard of care (excluding complement inhibitors).
        - Pegcetacoplan demonstrated superiority in the co-primary endpoints of hemoglobin stabilization and LDH reduction compared to standard of care. Hemoglobin stabilization was defined as less than 1g/dL decrease in hemoglobin levels in the absence of blood transfusions.

        - In addition, more patients on pegcetacoplan were transfusion-free compared to standard of care. 91% of patients on pegcetacoplan were transfusion free compared to 6% on standard of care.

- *Fabhalta (iptacopan)* was studied in two 24- week, open- label, phase III trials. APPLY-PNH compared Fabhalta (iptacopan) to C5 inhibitors in patients with residual anemia despite C5 inhibitor treatment. At baseline, a majority of patients had at least one transfusion in the 6 months prior to the trial. APPOINT-PNH was a single-arm trial that enrolled complement inhibitor-naïve patients; however, applicability is limited as a majority of patients were enrolled in China.[5 7]
    * Treatment with Fabhalta (iptacopan) resulted in statistically significant and clinically meaningful improvements in the hemoglobin level from baseline as well as greater avoidance of transfusions.
- *Voydeya (danicopan)* was studied in the ALPA trial as add-on to C5 inhibitors (eculizumab or ravulizumab) and was compared to placebo plus C5 inhibitors in patients with persistent anemia despite C5 inhibitor therapy.[6 8]
    * Treatment with add-on Voydeya (danicopan) resulted in statistically significant and clinically meaningful improvements in hemoglobin levels from baseline as well as greater avoidance of transfusions at 24 weeks versus placebo.
    * Known safety profile appears to be generally consistent with other complement inhibitors but long-term data is lacking in the setting of potential additive toxicity due to inhibition of both complement and proximal pathways.

<u>Atypical hemolytic uremic syndrome (aHUS)</u>

- The best available evidence for Soliris (eculizumab) in aHUS is limited to four phase 2, open-label, non-randomized, prospective, single-arm studies in populations. Two of the studies are not published at this time.
    * One study (n=17) in adolescent and adult patients who were resistant to plasma therapy and had impaired kidney function found a mean increase in platelet counts from baseline after treatment with Soliris (eculizumab) for a median length of 64 weeks. [17 50]
    * One study (n=20) in adolescent and adult patients with chronic renal impairment and no evidence of thrombotic microangiopathy found that 80% of patients treated with Soliris (eculizumab) achieved a thrombotic microangiopathy activity event-free status (defined as ≤ 25% decrease in platelet count and no plasma therapy, or new dialysis for ≥ 12 consecutive weeks). [17 50]
    * Two unpublished studies measured thrombotic microangiopathic (TMA) response in pediatrics (n=22) and adults (n=41), defined as hematological normalization and ≥ 25% improvement in serum creatinine from baseline. After a minimum of 26 weeks of treatment with Soliris (eculizumab), 64% of pediatric patients and 56% of adult patients achieved the primary endpoint. [17]
    * Reduction in mortality and other clinically meaningful endpoints have not yet been studied in a controlled clinical trial.

- The evidence for Ultomiris (ravulizumab-cwvz) for aHUS limited to two open-label, non-randomized, prospective, single-arm trials (one in adults, n=56; one in pediatric patients, n=16). [11]
    * Both trials assessed Complete TMA Response during the 26-week trial, defined as normalization of hematological parameters (platelet count and LDH) and ≥ 25% improvement in serum creatinine from baseline.
    * After a minimum of 26 weeks of treatment with Ultomiris (ravulizumab-cwvz), 71% of pediatric patients and 54% of adult patients achieved the primary endpoint.
    * The efficacy results are overall similar to trials of Soliris (eculizumab) for aHUS.
- Additional published studies that support the use of Soliris (eculizumab) and Ultomiris (ravulizumab-cwvz) in aHUS are limited to case studies and retrospective reviews.
- All studies of complement inhibitors in aHUS have significant limitations including an absence of control groups, open-label treatment, ambiguous recruitment techniques, and use of surrogate markers as primary endpoints. As such, the true benefit of Soliris (eculizumab) in aHUS is unclear and results should be interpreted with caution.
- There is interest in the use of higher doses of Ultomiris (ravulizumab-cwvz) for patients with incomplete control of symptoms. However, there is no data to support the safety and efficacy of dosing Ultomiris (ravulizumab-cwvz) more frequently than every 8 weeks in patients greater than 20 kg. There is insufficient evidence to establish the safety or efficacy for the use of Soliris (eculizumab) and/or Ultomiris (ravulizumab-cwvz) after kidney transplantation for patients with recurrent aHUS or other micro thrombotic condition-associated renal failure.
- There are no nationally published guidelines for the treatment of aHUS. National Health Service England has commissioned Soliris (eculizumab) for patients newly diagnosed with aHUS and for existing patients who are on dialysis and are suitable for a kidney transplant until a guideline is developed. [17]

<u>Refractory myasthenia gravis (MG)</u>

- The evidence for complement inhibitors in MG is limited. In the pivotal phase 3 trials of Soliris (eculizumab), Ultomiris (ravulizumab-cwvz), and Zilbrysq (zilucoplan), the active treatment arm improved functional scores in patients with refractory generalized MG compared to placebo [REGAIN [51] for Soliris (eculizumab), CHAMPION-MG [52] for Ultomiris (ravulizumab-cwvz), and RAISE [53] for Zilbrysq (zilucoplan)], a surrogate for MG symptoms.
    * Patients in who were included in the efficacy analyses of pivotal trials had a MG severity classification of MGFA Class II to IV, MG-ADL score 6 or higher, and positive serologic test for anti-AChR antibodies.
    * In addition, patients in REGAIN failed ≥2 ISTs or ≥1 IST and required chronic plasma exchange or IVIG for over 1 year. 98% of patients were on ≥2 ISTs and 52% of patients were on ≥3 ISTs for an average length of 2.5 to 7.3 years prior to enrollment. Patients in CHAMPION-MG and RAISE were not required to have prior therapies.

    * In REGAIN, the primary endpoint was the mean difference of scores from baseline to week 26 of MG-ADL measured by worst-rank ANCOVA, which showed Soliris (eculizumab) was not significantly better than placebo (p=0.0698). FDA-approval was based on non-primary sensitivity analysis outcomes with statistical significance but the magnitude of mean total score differences were insufficient to represent clinically meaningful improvement. However, it should be noted that several subjects left the trial for reasons unrelated to their MG, which affected the statistical analysis of the worst-rank ANCOVA.
    * The primary endpoint of change from baseline in MG-ADL score to week 26 was met in CHAMPION-MG. Ultomiris (ravulizumab-cwvz) also demonstrated improvements in MG-ADL muscle strength, and quality life, sustained through 60 weeks in an open-label extension.
    * The primary endpoint of change from baseline in MG-ADL score to week 12 was met in RAISE; the results represented both clinically meaningful and statistically significant improvements from baseline. Zilbrysq (zilucoplan) also demonstrated improvements in QMG score.
    * Soliris (eculizumab), Ultomiris (ravulizumab-cwvz), and Zilbrysq (zilucoplan) have not been studied in patients with less severe MG, including patients with MFGA Class I or those responding to IST therapy. In addition, there is no evidence for the use in patients in myasthenic crisis (Class V).

Neuromyelitis Optica Spectrum Disorder (NMOSD)

- The evidence for Soliris (eculizumab) in NMOSD is limited. One phase 3, time-to-event trial showed that Soliris (eculizumab) reduced the frequency of first adjudicated relapse compared to placebo (PREVENT).[26]
    * Patients enrolled in the trial had “highly active” disease defined as two relapses in the past year or three relapses in the past two years, with one of those in the last year; baseline annualized relapse rate was 2, median Expanded Disability Status Scale (EDSS) 4; 76% of patients were on immunosuppressive therapy at baseline and 32% had previous rituximab treatment.
    * In PREVENT, the primary endpoint of first adjudicated relapse occurred in 3% of the Soliris (eculizumab) arm versus 43% in the placebo arm, HR 0.06 [95% CI 0.02 to 0.20]. At 144 weeks, 96.5% of patients in the Soliris (eculizumab) group and 45.4% in the placebo group remained relapse- free.
    * Key secondary endpoints included change from baseline in functionality and patient-reported health outcomes as measured by EDSS as well as the modified Rankin Scale, Hauser Ambulation Index, and EQ-5D-3L. The first measure, EDSS, did not reach statistical significance. However, the remaining measures trended in favor of the treatment group.
- The evidence for Ultomiris (ravulizumab-cwvz) in NMOSD is limited to one phase 3, open-label, external control trial (N=58), CHAMPION-NMOSD[54], that demonstrated Ultomiris (ravulizumab-cwvz) reduced the frequency of first adjudicated relapse compared to historical control (placebo arm of the PREVENT trial).
    * No patients taking ravulizumab (n = 58) had an adjudicated relapse (during 84.0

patient-years of treatment) versus 20 patients with adjudicated relapses in the placebo group of PREVENT (during 46.9 patient-years; relapse risk reduction = 98.6%, 95% confidence interval = 89.7%–100.0%, p < 0.0001).

- Guidelines recommend treatment of acute episodes/ relapse and use of maintenance immunosuppressive therapy (IST), to reduce the frequency of relapse). [25 28 31 32 55]
    * Treatment of Relapse: Patients are usually treated with 1 g of intravenous (IV) methylprednisolone (IVMP) for 3–5 days. Relapses that do not respond to IV steroids may benefit from five to seven plasma exchange (PLEX) procedures over a 2-week period. Oral prednisone (1 mg/kg) for 1–6 months can be initiated after IVMP or PLEX to ensure a prolonged effect on inflammation until steroid-sparing immunosuppressants take effect.
    * Maintenance Therapy: A variety of immunosuppressive therapy (IST) are regarded by many clinicians as first-line therapy based on primarily observational or single-arm data. The most widely prescribed treatments include corticosteroids, azathioprine, mycophenolate mofetil, and rituximab. The use of azathioprine and mycophenolate mofetil has fallen out of favor due to lack of efficacy. However, if given, they are often prescribed with low doses of corticosteroids. Rituximab has evidence for reduction of relapse rates and disability in NMO, based on one RCT (n=68) and dozens of case series, including in patients who fail oral immunosuppressive treatments. [30 32-35] Paradoxical relapses may occur shortly after initiation of rituximab therapy so it is important to allow enough time for the rituximab to become effective. Complete suppression of CD19+B lymphocytes takes one month. [35]

<u>CD55-defiecent protein-losing enteropathy (CHAPLE disease)</u>

- The evidence for use of Soliris (eculizumab) in CHAPLE disease is limited to one small observational study of 16 patients with a confirmed CD55 loss of function mutation and severe CHAPLE disease manifestations requiring frequent hospitalizations, albumin, and immunoglobulin transfusions.[56]
    * Patients received Soliris (eculizumab) off label, with treatment effects observed over an average of 20 months.
    * All patient achieved normalization of their serum albumin within 2-4 weeks and remained normal for 6 months or longer.
    * The majority patients (12 of 16) no longer required any hospitalizations or transfusions, and most previous treatment interventions became unnecessary.
    * Although the evidence is of lower quality (non-controlled), Soliris (eculizumab) is the standard of care treatment option for patients with severe CHAPLE disease manifestations requiring frequent hospitalizations, albumin, and immunoglobulin transfusions.
- The evidence for Veopoz (pozelimab) obtaining FDA approval is limited to the ongoing 1878 trial (n=10), a small, phase 2/3, international, multicenter, open-label, single arm trial , of patients with confirmed, active CHAPLE disease.[36 57]

    * The trial included only patients with genetically confirmed (CD55 loss of function mutation) and symptomatic CHAPLE disease with a serum albumin of <3.2 g/dl (baseline average was 2.18 g/dl).
    * A control was generated using the patients pretreatment medical histories to compare to post-treatment with Veopoz (pozelimab).
    * Patients received a 30 mg/kg loading dose of Veopoz (pozelimab) on day 1, followed by 10 mg/kg weekly thereafter for up to 144 weeks.
    * All patients (10/10) achieved the primary efficacy endpoint of normalized serum albumin (≥3.5 g /dl) by week 12 and maintained it through week 72 at the most recent analysis.
    * Secondary endpoints supporting efficacy were the decrease in hospitalization days post treatment (268 days prior to treatment vs only 7 after treatment) and total number of albumin transfusions pre and post treatment (60 vs 1).
- Although both Soliris (eculizumab) and Veopoz (pozelimab) have shown some efficacy in CHAPLE disease, the available evidence for efficacy is of low quality for both. However, there is significantly more safety experience with Soliris (eculizumab) with years of real-world use and is significantly less costly than Veopoz (pozelimab). Therefore, the use of Veopoz (pozelimab) for patients with confirmed CHAPLE disease is coverable only in patients who have had an insufficient response or intolerance to Soliris (eculizumab).

Antineutrophil cytoplasmic antibody-associated vasculitis (ANCA-AV) (MPA or GPA) [37 39 41]

- The evidence for Tavneos (avacopan) obtaining FDA approval was based on one phase 3 trial. The trial was a double-blind active-controlled RCT (ADVOCATE) concluding that Tavneos (avacopan) was non-inferior to standard of care for induction and maintenance of remission in patients with ANCA-AV (MPA or GPA) (n=331). Given the lack of superior benefit versus the standard of care, and availability of effective lower-cost treatment options, the use of Tavneos (avacopan) is coverable only in patients with severe active ANCA-AV (GPA or MPA) who have previously failed standard induction therapy or relapsed since achieving remission in the past 12 months.
    * Patients enrolled in the trial had either newly diagnosed active severe ANCA-AV (69%) or relapsed active severe ANCA-AV (31%). Active severe ANCA-AV is defined by ACR guidelines as new, persistent, or worsening clinical signs or symptoms attributed to GPA or MPA that has organ or life-threatening manifestations.
    * In the trial these patients had to have one major Birmingham Vasculitis Activity Score (BVAS) item, 3 non-major items, or two renal items of hematuria and protein urea. BVAS is the clinical trial standard measure for ANCA-AV remission scoring with score of 0 being complete remission. The average BVAS score in both arms was 16.3, which indicates active severe disease.
    * The breakdown of patients with GPA vs MPA in the trial was 55% to 45%, respectively. Patients that had EGPA were excluded from this trial as EPGA is clinically and pathologically different and is therefore excluded from trials involving ANCA-AV.

* Patients were randomized to Tavneos (avacopan) or 20-week steroid taper in addition to investigator-choice standard of care induction therapy with rituximab or cyclophosphamide. Patients in both arms were still allowed to receive additional non-study supplied steroids. In addition, the patients who received oral or IV cyclophosphamide received standard of care maintenance therapy with azathioprine beginning at week 15 till week 52, while the rituximab patients received no standard of care maintenance treatment.
    - 36% of patients in each arm received cyclophosphamide.
    - 65% of patients in each arm received rituximab.
* Primary endpoints were remission at week 26 (BVAS of 0) and sustained remission at week 52 (BVAS of 0).
* Results of the ADVOCATE trial showed that the Tavneos (avacopan) arm of the trial was non-inferior to standard of care at inducing remission and sustaining remission at week 52. Tavneos (avacopan) only showed superiority when compared to placebo (not standard of care) at week 52. The trial failed to prove superiority and only showed non-inferiority when compared to current standard of care. As a result, the FDA approved labeled indication for Tavneos (avacopan) is for add-on therapy only.
* Factors which may impact the accuracy, applicability, and generalizability of the results for this trial include but are not limited to the following:
    - During the study, 86% of the Tavneos (avacopan) arm and 90% of the steroid arm received non-study supplied steroids.
    - The patients who received azathioprine for standard of care maintenance of remission treatment showed no difference between Tavneos (avacopan) and placebo at week 52.
    - Patients' response to Tavneos (avacopan) based on investigator BVAS scale scoring supported only non-inferiority when compared to placebo at week 52.
    - Secondary endpoints of this study included a novel glucocorticoid toxicity index scoring tool (GTI), that was determined by FDA to be not fit for its purpose and of no relevance to the benefit of avacopan in this trial. Other secondary endpoints included change in EGFR, quality of life measures (EQ-5D-5L and SF-36), and improvement of urinary albumin to creatinine ratio, all of which provide no clinical meaningful treatment benefit of Tavneos (avacopan) and were not adjusted for multiplicity.
* Sub-group analysis in patients treated with Tavneos (avacopan) who were newly diagnosed (69%) compared to the patients who had relapsed (31%), showed significant difference in the response to Tavneos (avacopan). The newly diagnosed patient's response rate of Tavneos (avacopan) compared to the prednisone arm was 66.1% vs 66.7% at week 26 and 60.9% vs 57.9% with neither being significant. Whereas the relapsed patients showed a much higher response rate to Tavneos (avacopan) compared to prednisone of 86.3% vs 78% at week 26 and 76.5% vs 48% at week 52.

- Given the lack of evidence to establish Tavneos (avacopan) is superior to placebo as add-on to current standard of care, and the availability of effective lower-cost treatment options, the use of Tavneos (avacopan) for severe active ANCA-associated vasculitis will only be coverable in patients who have previously failed standard induction therapy or have relapsed since achieving remission in the past 12 months.

Investigational Uses

- Soliris (eculizumab) has been studied in a variety of other conditions. Due to lack of published data, lack of high-quality data, or lack of positive data these conditions are considered investigational. [58-65]
- There is interest in the use of Ultomiris (ravulizumab-cwvz) for patients with recurrent IgA nephropathy. However, there is there is insufficient evidence to establish the safety or efficacy of Ultomiris for IgA nephropathy. Trials are ongoing.[65]
- One Phase 2/3 trial (PROTECT) evaluated Soliris (eculizumab) versus placebo in kidney transplant patients at high risk of delayed graft function (DGF). The trial failed to show a statistically significant difference in the incidence of DGF, death, graft loss, or discontinuation at seven days following a transplant (35.9% in Soliris (eculizumab) vs. 41.7% in placebo, p = 0.398). [65]
- Ultomiris (ravulizumab-cwvz), another complement inhibitor, is not coverable for other indications, except as listed in the coverage criteria. Despite being a derivative of Soliris (eculizumab), there is insufficient evidence at this time to establish the safety or efficacy of Ultomiris (ravulizumab-cwvz) for other indications, including MG. In addition, the dose of Ultomiris (ravulizumab-cwvz) for other indications is unknown.
- An intravitreal formulation of pegcetacoplan (Syfovre) is now available for geographic atrophy secondary to age-related macular degeneration (AMD). There is no evidence for use of IV pegcetacoplan (Empaveli) for AMD.
- Tavneos (avacopan) has been studied in a variety of other conditions including aHUS and C3 glomerulonephritis. Due to lack of published and positive data, these conditions are considered investigational. [66 67]
- Veopoz (pozelimab) is being studied in a variety of other conditions including PNH and MG. Due to lack of published and positive data, use of Veopoz (pozelimab) in these conditions is considered investigational.[36]
- Although Fabhalta (danicopan) was studied in C5-inhibitor naïve PNH, the study was of poor quality (N=40, single-arm) with limited applicability to patients in the United States (half were from China, which has different standards of care).[7]

Safety [11 57 60 68]

- Complement inhibitors (as listed in *Table 1*) all carry a boxed warning for life-threatening and fatal meningococcal infections. Patients should be immunized with a meningococcal vaccine at least 2 weeks prior to the first dose of complement inhibitors (as listed in *Table 1*) unless the risks of delaying complement inhibitor therapy outweigh the risks of developing a meningococcal infection.
- There is a Risk Evaluation and Mitigation Strategy (REMS) program in place for Empaveli (pegcetacoplan), Fabhalta (iptacopan), Soliris (eculizumab), Ultomiris

(ravulizumab-cwvz), Voydeya (danicopan), and Zilbrysq (zilucoplan). The purpose of the REMS program is to mitigate the occurrence and morbidity associated with meningococcal infections. Providers must be certified by the REMS program to prescribe complement inhibitors.

- There was one death related to Soliris (eculizumab) in clinical trials. The patient was part of the PREVENT trial for NMOSD and died due to pulmonary empyema.
- In trials, there was a higher incidence of hepatoxicity, hypersensitivity, and hepatitis B virus (HBV) reactivation with use of Tavneos (avacopan) compared to standard of care. Patients should be screened prior to initiation of treatment as well as monitored throughout treatment.

Administration and Dosing [11 60 69]

- Supplemental dosing: Some interventions such as plasma exchange/plasmapheresis (PLEX), fresh frozen plasma (FFP), and intravenous immunoglobulin (IVIg), have been shown to reduce eculizumab or ravulizumab serum levels.
    * In patients with aHUS or MG receiving concomitant PLEX or FFP, supplemental dosing, and frequency of Soliris (eculizumab) varies.
    * Supplemental dosing for Ultomiris (ravulizumab-cwvz) in the setting of PLEX and IVIG also varies, based on the most recent dose of Ultomiris (ravulizumab-cwvz) and the intervention.
    * Of note: use of ongoing maintenance IVIG therapy, in combination with maintenance complement inhibitor therapy is considered investigational, beyond a transition period.
- Soliris (eculizumab): For breakthrough hemolysis in PNH:
    * Soliris (eculizumab) dosing may be adjusted to 900 mg every 12 days instead of every 14 days. In the pivotal trial for the FDA labeled dose, 900 mg every 14 days, plus or minus 2 days, was used, such that 900 mg every 12 days is considered coverable per label, when there is breakthrough hemolysis.
    * There is also limited data that doses of 1200 mg every 14 days have been used for breakthrough; however, since it is more costly without proven benefit over 900 mg every 12 day dosing, it is considered 'not medically necessary.' [70 71]
    * No additional benefit is observed above the recommended dose.
- Empaveli (pegcetacoplan):
    * For lactate dehydrogenase (LDH) levels greater than 2 × the upper limit of normal (ULN), Empaveli (pegcetacoplan) dose may need to be adjusted to 1,080 mg every three days based on limited data. [69]

Cross References
Site of Care Review, Medication Policy Manual, Policy No. dru408
Products with Therapeutically Equivalent Biosimilars/Reference Products, Medication Policy Manual, Policy No. dru620
Enspryng, satralizumab, Medication Policy Manual, Policy No. dru656
Uplizna, inebilizumab, Medication Policy Manual, Policy No. dru657
Efgartigimod-containing medications, Medication Policy Manual, Policy No. dru696
Complement Inhibitors for the Eye, Medication Policy Manual, Policy No. dru762

Codes	Number	Description
HCPCS	J1300	Injection, eculizumab (Soliris), 10 mg
HCPCS	J1303	Injection, ravulizumab-cwvz (Ultomiris), 10 mg

Appendix 1: Medications that may unmask or worsen myasthenia gravis *[58]
Aminoglycosides
Amantadine
Anti-arrhythmics (procainamide, propafenone, quinidine)
Antiepileptics (various, carbamazepine, gabapentin, phenytoin, etc.)
Cancer immunotherapies, including but not limited to: Anti-programmed death receptor-1 monoclonal antibodies (PD1s, PDL-1s; Opdivo [nivolumab], Keytruda [pembrolizumab], etc.) Yervoy (ipilimumab) Provenge (sipuleucel-T)
Antihistamines (diphenhydramine)
Beta-blockers
Calcium channel blockers (felodipine, verapamil)
Colchicine
Erythromycins (azithromycin, clarithromycin, clindamycin)
Plaquenil (hydroxychloroquine)
Interferons (various)
Lithium
Magnesium
Neuromuscular blockers (succinylcholine, etc.)
Opioids
Phenothiazines (haloperidol)
Proton pump inhibitors (lansoprazole, omeprazole)
Quinine
Quinolones (ciprofloxacin, levofloxacin, etc.)
Statins (pravastatin, etc.)

*Including, but not limited to this list. Medication lists will be reviewed in full versus compendium (such as DrugDex).

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Revision History

Revision Date	Revision Summary
6/20/2024	• Added Fabhalta (iptacopan) and Voydeya (danicopan) for treatment-experienced PNH. • Fabhalta (iptacopan) for treatment-naïve PNH is investigational due to poor quality of evidence. • High-dose Soliris (eculizumab) modified to not medically necessary (NMN), as several options are now available for breakthrough PNH. • Removed Empaveli (pegcetaoplan) ST through Ultomiris (ravulizumab) in treatment naïve PNH to align with standard of care.
3/21/2024	Readded weight specification to *Table 2* Initial Authorization dosing for NMOSD.
12/7/2023	• Added newly FDA-approved Veopoz (pozelimab) to policy. Limits coverage to patients diagnosed with genetically confirmed CHAPLE disease by a specialist, when previous treatment with Soliris (eculizumab) has been ineffective or not tolerated. • Added Zilbrysq (zilucoplan) to policy for generalized myasthenia gravis (gMG). • Simplified coverage criteria for gMG. The baseline MG-ADL score was updated to "6 or more" to match trial criteria and the prior therapy requirement was simplified to at least ONE neonatal Fc receptor (FcRn) antagonist and thymectomy. • Authorization duration extended to 6 months for initial and 12 months for reauthorization for all medications in this policy,
9/13/2023	• Coverage criteria updated to allow for subcutaneous (SC) injection of Ultomiris (ravulizumab) for PNH and aHUS. • Coverage added for:

Revision Date	Revision Summary
	- Ultomiris (ravulizumab) IV for NMOSD. Soliris (eculizumab) will now require step therapy (ST) with Ultomiris (ravulizumab), Enspryng (satralizumab) AND Uplizna (inebilizumab). - Supplemental dosing of Ultomiris (ravulizumab) or Soliris (eculizumab) after plasma exchange or IVIG. • Use of Empaveli (pegcetacoplan) in macular degeneration remains investigational, as an intravitreal formulation, Syfovre (pegcetacoplan intravitreal) is available.
9/23/2022	Coverage criteria updated to add additional step therapy (ST) for Soliris (eculizumab) as follows: • aHUS: Ultomiris (ravulizumab) • gMG: Vyvgart (efgartigimod) AND Ultomiris (ravulizumab) • PNH: Empaveli (pegcetacoplan AND Ultomiris (ravulizumab) • NMOSD: Enspryng (satralizumab) AND Uplizna (inebilizumab)
6/17/2022	Added coverage criteria for Ultomiris (ravulizumab-cwvz) for use in generalized myasthenia gravis (gMG).
3/18/2022	• Added the newly FDA-approved Tavneos (avacopan) to policy. Limits coverage to patients with severe active ANCA-AV as adjunctive therapy with standard of care including glucocorticoids, when managed by a specialist and previous standard of care therapies (rituximab, cyclophosphamide, glucocorticoids, MTX, AZA, and MMF) were ineffective at inducing or maintaining remission. • Updated MG-ADL score to greater than or equal to 5, to match Vyvgart (efgartigimod) policy. • Added combination use with Vyvgart (efgartigimod) to investigational uses.
10/15/2021	Added the newly FDA-approved Empaveli (pegcetacoplan) to policy. Coverage for paroxysmal nocturnal hemoglobinuria (PNH) will align with current coverage criteria for Soliris (eculizumab) and Ultomiris (ravulizumab-cwvz).
7/16/2021	• Continuation of therapy (COT) language updated to align with Enspryng (satralizumab) and Uplizna (inebilizumab). • Added quantity limit (QL) for Soliris (eculizumab) when used for PNH with breakthrough hemolysis. • Clarified use of combination therapy for NMOSD as "Investigational" (removed from medical necessity criteria). No changes to intent of coverage criteria with this annual update.

Revision Date	Revision Summary
1/20/2021	• Updated COT language to new format. • Reformatted quantity limits for operational ease. No change to intent.
10/28/2020	• Added additional step with either Enspryng (satralizumab) or Uplizna (inebilizumab) for Soliris (eculizumab) in NMOSD. • Updated Soliris (eculizumab) NMOSD criteria to limit concomitant use with rituximab, Enspryng (satralizumab) or Uplizna (inebilizumab).
6/15/2020	Continuation of therapy (COT) language added. Removed references to brand Rituxan to account for preferred/non-preferred changes in biosimilars policy (dru620).
10/23/2019	Effective 11/15/2019: • Added coverage criteria for neuromyelitis optica spectrum disorder (NMOSD) for Soliris (eculizumab). • Added coverage criteria for aHUS for Ultomiris (ravulizumab-cwvz). • Updated associated investigational uses for Ultomiris (ravulizumab-cwvz).
4/24/2019	• Renamed policy "Complement Inhibitors" • Criteria added for newly-approved Ultomiris (ravulizumab-cwvz) for PNH. • Updated previous Soliris (eculizumab) criteria for HUS to add nephrology specialty and clarify coverage criteria.
3/19/2018	Effective 4/1/2018: • Added coverage criteria for myasthenia gravis. • Updated associated investigational uses. Effective 7/1/2018: Align re-authorization to biannual (every 24-weeks) for all indications.
1/13/2017	Updated quantity limit. Added additional investigational uses.
11/11/2016	Removed site of care language from the individual drug policy; however, requirements still apply. Reference to *Site of Care Review*, dru408 is provided as part of criterion I.A.
1/08/2016	Annual update, no changes to criteria.
1/19/2015	New policy.

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Medication Policy Manual | **Policy No:** dru388

Topic: Blincyto, blinatumomab | **Date of Origin:** March 13, 2015

Committee Approval Date: December 12, 2024 | **Next Review Date:** 2025

Effective Date: January 15, 2025

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Blincyto (blinatumomab) is an immunotherapy used in the treatment of B-cell precursor acute lymphoblastic leukemia (ALL). It is given via continuous intravenous infusion over 28 days in six-week cycles. Hospitalization is recommended when starting the infusion to monitor for severe adverse effects.

Policy/Criteria

Most contracts require pre-authorization approval of Blincyto (blinatumomab) prior to coverage.

I. Continuation of therapy (COT): Blincyto (blinatumomab) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Blincyto (blinatumomab) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A and B below are met.

A. A diagnosis of **B-cell precursor, CD19-positive acute lymphoblastic leukemia** (ALL).

AND

B. Blincyto (blinatumomab) is administered in one of the following settings (1 or 2):

1. Refractory/relapsed: After at least one prior ALL therapy has been ineffective (relapsed or refractory disease).

OR

2. In complete remission: The ALL is in a first or second complete remission (CR).

NOTE this includes use of Blincyto as "consolidation therapy" and use for "MRD-positive disease (after induction chemotherapy)".

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Blincyto (blinatumomab) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Blincyto (blinatumomab) may be authorized in the following quantities:

1. For Relapsed or refractory B-cell ALL:

a. ***Initial Authorization:*** Five, 28-day infusions (induction and consolidation).

b. ***Reauthorization:*** If remission is achieved with the initial induction and consolidation cycles, up to four additional, 28-day infusions (maintenance) may be authorized.

2. For B-cell ALL in complete remission:

a. ***Initial Authorization:*** Up to four, 28-day infusions may be authorized.

b. ***Reauthorization:*** No additional treatment courses will be authorized beyond four, 28-day infusions

IV. Blincyto (blinatumomab) is considered investigational when used for all other conditions, including but not limited to diffuse large B-cell lymphoma.

Position Statement

- Blincyto (blinatumomab) is an immunotherapy that targets CD-19-positive B-cells (precursor B-cells). It is indicated for the treatment of CD19-positive B-cell precursor acute lymphoblastic leukemia (ALL) in several settings:
  - Relapsed after, or refractory to, prior therapy
  - After a complete remission (CR) is achieved with multiagent chemotherapy induction:
    - When minimal residual disease (MRD) is detected
    - When used in the consolidation phase, including for MRD-negative disease and/or prior to hematopoietic stem cell transplant (HSCT).
- It is not indicated for mature B-cell (CD-20-positive) ALL. Other therapies are used in treating this ALL subtype.
- *Detection of minimal residual disease*: In clinical trials of Blincyto (blinatumomab), MRD was determined based on reverse transcriptase-polymerase chain reaction (PCR) or flow cytometry. Current standard of care for determination of MRD now also includes use of FDA-approved next generation sequencing (NGS)-based assays, such as clonoSEQ, for detection of lower levels of MRD.
- Based on its mechanism of action, there is interest in using Blincyto (blinatumomab) in other cancers; however, there is currently no evidence supporting its safety and effectiveness in any other condition.
- Potentially serious and life-threatening reactions including Cytokine Release Syndrome and neurological toxicities have been reported with Blincyto (blinatumomab).

- Blincyto (blinatumomab) is given as a continuous intravenous infusion for 28 days (one cycle). A minimum of a 2-week treatment-free interval is recommended between cycles. The dosing and schedule depends on the B-cell ALL setting in which it is used. Hospitalization is recommended when initiating the first two cycles to monitor for potentially life-threatening adverse effects.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy

B-cell precursor ALL, after complete remission with chemotherapy induction

- Blincyto (blinatumomab) has been studied and shown to be effective for two B-cell precursor ALL settings after complete remission (CR/CRi) from induction therapy with multiagent chemotherapy:
    * For the eradication of MRD (treatment of MRD-positivity, after induction with multiagent chemotherapy)
    * Use of consolidation therapy (in MRD-negative patients, after induction with multiagent chemotherapy).

    Both these settings are part of the "consolidation phase," after which patients may go on to treatment with a hematopoietic stem cell transplant (HSCT).
- For this policy, "complete remission" is considered as either one of the following:
    * hematologic complete remission (CR) or
    * CR with incomplete peripheral blood count recovery (CRi)
- For patients with complete remission (CR/CRi) after induction with multiagent chemotherapy, choice of next treatment is based on presence of minimal residual disease (MRD). However, definition in clinical practice may vary from the definition used in

clinical trials. Therefore, patients who were considered MRD-negative in the context of a clinical trial may in fact be considered MRD-positive, due to the use of more sensitive testing in clinical practice (See *Detection of Minimal Residual Disease* below).

- Therefore, this policy considers Blincyto (blinatumomab) to be considered for coverage under the criteria for patients who achieved CR/CRi with induction ("complete remission after the first or second relapse"), at the treatment is used as a part of the consolidation phase of treatment, independent of the MRD-status after induction with multiagent chemotherapy.

B-cell precursor ALL in the Consolidation Phase of multiphase chemotherapy

The evidence for expansion of the FDA indication included the following two trials:

- A phase 3 multicenter, open-label, randomized controlled trial [E1910] evaluated the addition of Blincyto (blinatumomab) to standard consolidation chemotherapy in adult patients with Philadelphia chromosome-negative (*BCR::ABL1*-negative) B-cell precursor ALL who achieved a complete response after induction and intensification chemotherapy (n=224).[1]
    * All patients evaluated in the trial were MRD-negative disease after induction and intensification chemotherapy. In the initial trial design, patients with MRD-positive status also underwent randomization. After the approval of blinatumomab therapy for patients with MRD-positive status, a protocol amendment assigned all subsequent patients with MRD-positive status to the blinatumomab group (n=18). However, the primary endpoint excluded the assessment of MRD-positive patients.
    * Patients were randomized to one of the following:
        o Two cycles of Blincyto (blinatumomab), followed by four cycles of chemotherapy, then two cycles of Blincyto (blinatumomab)
        o Four cycles of consolidation chemotherapy.
    * The primary endpoint, overall survival (OS) at 3 years, was higher in the Blincyto (blinatumomab) arm (85%) than the chemotherapy arm (68%).
- A phase 3 multicenter, open-label, randomized controlled trial [Study 20120215] evaluated the addition of Blincyto (blinatumomab) to standard consolidation chemotherapy in pediatric patients with Philadelphia chromosome-negative, high-risk, first relapse B-cell precursor ALL who achieved a complete response after induction (n=108). [2]
    * All enrolled patients had completed induction chemotherapy and had a response [M1 marrow (<5% morphologic blasts or M2 marrow (>5% but <25% morphologic blasts)].
    * All enrolled patients received the first 2 cycles of standard consolidation chemotherapy, then were randomized to a treatment arm for the third (and final) consolidation treatment.
        o Blincyto (blinatumomab) 15 µg/m2 /day for 4 weeks by continuous IV infusion for one cycle

- One cycle of consolidation chemotherapy (to complete three cycles)

  Each group went on to receive HSCT (if the patient achieved a complete remission from consolidation therapy).

* The primary endpoint, event-free survival (EFS), was higher in the Blincyto (blinatumomab) arm (69%) than the chemotherapy arm (43%).

Evidence from two additional trials support the use of Blincyto (blinatumomab) in the consolidation phase:

- One open-label, single arm phase 2 trial (BLAST) in adult patients in the first or later CR, with persistent MRD (See "*MRD-positive B-cell precursor ALL*" below). [3]
- A phase 3 open-label, randomized controlled trial [COG AALL1331] evaluated the Blincyto (blinatumomab) versus standard induction chemotherapy in pediatric patients with Philadelphia chromosome-positive, high-risk, first relapse B-cell precursor ALL (n=255).[4] (This trial is also confirmatory of the "*MRD-positive B-cell precursor ALL*" indication below)
  * All enrolled patients received a 4-week reinduction standard chemotherapy course, then were randomized to a treatment arm for the consolidation treatment.
    - Two cycles of Blincyto (blinatumomab)
    - Two cycles of multiagent chemotherapy

      Each group went on to receive HSCT.
  * After two cycles of blinatumomab, 2-year OS was 71.3% with blinatumomab vs. 58.4% with chemotherapy. Due to the encouraging treatment benefit observed, the trial was terminated early by the data and safety monitoring committee based.
  * Blincyto (blinatumomab showed) a trend toward improvement in DFS and OS, as well as lower toxicity, and better MRD clearance compared with chemotherapy in pediatric patients with B-cell ALL at first relapse
  * Of note: In the relapsed "low-risk" block of the AALL1331 trial, Blincyto (blinatumomab) was non-inferior to standard chemotherapy. [5]

MRD-positive B-cell precursor ALL

- A small, single-arm trial [MT103, BLAST] evaluated Blincyto (blinatumomab) in patients who achieved a complete remission after multiagent chemotherapy, but still had minimal residual disease (MRD) [n=113]. [3] The evidence is preliminary and approval in this setting is provisional (FDA Accelerated approval).
  * All patients enrolled in the trial were in either a first (71%) or a second (29%) hematologic complete remission with MRD.
  * MRD was detected by reverse transcriptase-polymerase chain reaction (PCR) or flow cytometry at a level of > 0.1% (using an assay with a minimum sensitivity of 0.01%).
  * All patients received Blincyto (blinatumomab) 15 µg/m2/day IV for up to 4 cycles. Patients could undergo HSCT any time after cycle 1

* Efficacy was based on the proportion of patients who achieved undetectable MRD within the first cycle of Blincyto (blinatumomab), and hematologic relapse-free survival (RFS).
    - Undetectable MRD was achieved by 70 of 86 patients (81.4%).
    - The median RFS was 22.3 months.
    - The rate of undetectable MRD and RFS was higher in patients who were in first remission than in those who were in second remission.
* Because there was no comparator in the study, it is not known if Blincyto (blinatumomab) improves any clinical outcome relative to the current standard of care (e.g., allogeneic stem cell transplant).

- More recently, the COG AALL1331 [4] was published and supports the indication (as discussed above in "*B-cell precursor ALL in the Consolidation Phase of multiphase chemotherapy*").

Detection of Minimal Residual Disease (MRD)

- Of note: Current standard of care for determination of MRD now also includes use of FDA-approved next generation sequencing (NGS)-based assays, such as clonoSEQ, for detection of lower levels of MRD. For patients with MRD based on PCR and/or flow cytometry, NGS testing is used for confirmation of MRD negativity.[6]
- Given the change in testing in clinical practice (versus testing used in the clinical trials), some patients with "MRD-negative" disease in a trial setting may be "MRD positive" in the clinical setting, with use of more sensitive NGS-based assays.

Relapsed or refractory B-cell precursor ALL

Philadelphia chromosome-negative B-cell precursor ALL:

In a multicenter, open-label randomized controlled trial [TOWER], Blincyto (blinatumomab) demonstrated improved overall survival (OS) relative to investigator's choice of chemotherapy in patients with relapsed or refractory Philadelphia chromosome-negative B-cell precursor ALL. Although an early survival advantage was apparent, there appeared to be little difference in survival between groups at 15 months which indicates the potential lack of a long-term benefit.[7]

- Subjects in the trial had disease in one of the following stages: refractory to primary induction or to salvage with intensive combination therapy, first relapse with first remission lasting fewer than 12 months, second or greater relapse, or relapse at any time after an autologous hematopoietic stem cell transplant.
- Median OS was 7.7 months in the Blincyto (blinatumomab) treatment arm and 4.0 months in the chemotherapy treatment arm (HR 0.71; 95% CI [0.55, 0.93]; p = 0.01. The median duration of follow up was 11.7 months.
- Because the survival curves converged by 15 to 18 months, there is some uncertainty regarding long-term benefits of this therapy.

Philadelphia chromosome-positive B-cell precursor ALL

A small, single-arm trial [ALACANTRA] evaluated complete remission rates achieved with Blincyto (blinatumomab) in patients with relapsed or refractory Philadelphia chromosome-positive B-cell precursor ALL. The design of this study is not suitable for evaluating efficacy because it lacks a comparator and employs an unvalidated surrogate endpoint.[8]

- All subjects (n=45) in the trial had prior therapy with TKIs directed against the Philadelphia chromosome [Gleevec (imatinib), Sprycel (dasatinib), Tasigna (nilotinib), or Iclusig (ponatinib)].
- Complete remissions were achieved in approximately 36% of subjects after induction with two cycles of Blincyto (blinatumomab).
- Although disease remission is one of the goals of treatment in ALL, this endpoint has not been validated to correlate with clinical outcomes such as improved symptom control, quality of life, or survival.
- Subsequently, the authors reported long-term durability with overall survival (OS) of 9 months, with a median 25.1 month follow up. Among patients with CR, the OS was 19.8 months.[9]

Treatment guidelines

The National Comprehensive Cancer Network (NCCN) ALL guideline lists: [NCCN][6]

- Initial Induction regimens - Standard front-line therapies:
  * Ph-negative B-cell precursor ALL: Multi-agent chemotherapy regimens.
  * Ph-positive B-cell precursor ALL: with tyrosine kinase inhibitors (TKIs) directed against the Philadelphia chromosome [Gleevec (imatinib), Sprycel (dasatinib), Tasigna (nilotinib), or Iclusig (ponatinib)].
- Consolidation therapy: For patients with complete remission (CR/CRi):
  * Choice of next treatment is based on presence of minimal residual disease (MRD). However, definition in clinical practice may vary from the definition used in clinical trials.
  * Blincyto (blinatumomab) is an option for both MRD-positive and MRD-negative patients
  * Hematopoietic stem cell transplant (HSCT) is an option for patients who achieve remission and have sufficient performance status.
- Relapsed/refractory B-cell precursor ALL: Blincyto (blinatumomab) is listed as follows:
  * Ph-negative: monotherapy

Ph-positive: either alone or in combination with a tyrosine kinase inhibitor.

OTHER CANCER SETTINGS AND CONDITIONS

There is interest in using Blincyto (blinatumomab) in other B-cell-mediated cancers; however, there is currently no good evidence to support its safety and effectiveness outside of the Ph-negative B-cell precursor ALL setting.

- A small, preliminary, observational trial evaluated response rates with Blincyto (blinatumomab) in 21 subjects with relapsed or refractory diffuse large B-cell lymphoma

(DLBCL). Further studies are needed to determine the optimal treatment strategy in this population. [10]

Safety [11]

- Package labeling for Blincyto (blinatumomab) includes a boxed warning for serious and potentially life-threatening or fatal Cytokine Release Syndrome (CRS) and neurological toxicity.
- The most common adverse effects (incidence of 20% or greater) reported with Blincyto (blinatumomab) in clinical trials included pyrexia, headache, peripheral edema, febrile neutropenia, nausea, hypokalemia, tremor, rash, and constipation.
- There is a Risk Evaluation and Mitigation Strategy (REMS) communication plan for Blincyto (blinatumomab) to inform healthcare providers of the following risks: Cytokine Release Syndrome, neurological toxicities, and preparation and administration errors.

Dosing [11]

- Blincyto (blinatumomab) is administered as a continuous intravenous infusion over 28 days (one cycle). Each cycle is followed by a 2-week treatment-free interval.
    * For r/r B-cell ALL: A treatment course consists of up 9 total cycles, with to two cycles for induction, three additional cycles for consolidation, and then up to four additional cycles of continued therapy (maintenance).
    * For B-cell precursor ALL, after complete remission with chemotherapy induction: up to 4 cycles, with variation on regimen based on treatment setting and plan for HSCT.
- Premedication with dexamethasone is recommended prior to each cycle. Blincyto (blinatumomab) package labeling recommends that initial doses of cycles one and two be administered in a hospital setting.
- General dosing parameters (refer to package insert for more specific information and pediatric dosing recommendations):

Cycle	Recommended dose	
	Patients ≥45 kg	**Patients < 45 kg**
Relapsed or refractory B-cell ALL		
Induction (cycle 1) Days 1 through 7: Days 8 through 28: Days 29 through 42:	 9 mcg/day 28 mcg/day 14-day treatment-free interval	 5 mcg/m2 /day (NTE 9 mcg/day) 15 mcg/m2 /day (NTE 28 mcg/day) 14-day treatment-free interval
Induction (cycle 2) Days 1 through 28: Days 29 through 42:	 28 mcg/day 14-day treatment-free interval	 15 mcg/m2 /day (NTE 28 mcg/day) 14-day treatment-free interval
Consolidation (cycles 3 to 5) Days 1 through 28: Days 29 through 42:	 28 mcg/day 14-day treatment-free interval	 15 mcg/m2 /day (NTE 28 mcg/day) 14-day treatment-free interval
Consolidation (cycles 6 to 9) Days 1 through 28: Days 29 through 84:	 28 mcg/day 56-day treatment-free interval	 15 mcg/m2 /day (NTE 28 mcg/day) 56-day treatment-free interval
B-cell ALL in the Consolidation Phase		
Days 1 through 28: Days 29 through 42:	28 mcg/day 14-day treatment-free interval	15 mcg/m2 /day (NTE 28 mcg/day) 14-day treatment-free interval
MRD-positive B-cell ALL		
Days 1 through 28: Days 29 through 42:	28 mcg/day 14-day treatment-free interval	15 mcg/m2 /day (NTE 28 mcg/day) 14-day treatment-free interval

Codes	Number	Description
HCPCS	J9039	Injection, Blinatumomab (Blincyto), 1 microgram

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10. Viardot A, Goebeler ME, Hess G, et al. Phase 2 study of the bispecific T-cell engager (BiTE) antibody blinatumomab in relapsed/refractory diffuse large B-cell lymphoma. *Blood*. 2016;127(11):1410-6. PMID: 26755709
11. Blincyto (blinatumomab) [package insert]. Amgen Inc.; Thousand Oaks, CA; June 2024.

Revision History

Revision Date	Revision Summary
12/12/2024	Effective 1/15/2025 • Add coverage criteria for B-cell ALL in the consolidation phase (new indication) and incorporation of new evidence.
12/7/2023	• No criteria changes with this annual review. • Clarification of coverage criteria, for operational consistency: o Removed 'Relapsed and refractory' prior to 'B-cell ALL' in criterion II.A. because it contradicts criterion B.2. (this does not impact the intent of the policy). o Simplified criterion for determination of MRD (to include NGS testing).
12/9/2022	• Updated standard language in policy. • Added 'CD19-positive' to the diagnosis required for coverage based on updated package labeling. • Removed requirement that Blincyto (blinatumomab) be used as monotherapy based on updated standards of care (it is now recommended in combination with tyrosine kinase inhibitors for Philadelphia chromosome-positive ALL).
1/20/2021	Updated continuation of therapy (COT) language. No changes to coverage criteria.
1/22/2020	Added continuation of therapy (COT) criteria (no change to intent of coverage criteria).
1/31/2018	There were no criteria changes with this annual update.
10/19/2018	• Added coverage for use in B-cell precursor ALL with MRD (new indication). • Updated quantity limitations and authorization section to include parameters for the new indication. • Updated the policy with new policy language (no change to intent).
9/8/2017	• Coverage of Blincyto (blinatumomab) was expanded to include patients with relapsed or refractory Philadelphia chromosome-positive B-cell precursor ALL based on new evidence in this population (it is now covered regardless of Philadelphia chromosome status). • Dosing limitations were updated to reflect new dosing recommendations (added maintenance cycles).
9/9/2016	Added diffuse B-cell lymphoma as an investigational condition.
3/13/2015	New policy.

Drug names identified in this policy are the trademarks of their respective owners.

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Medication Policy Manual | **Policy No:** dru390

Topic: Opdivo, nivolumab | **Date of Origin:** March 13, 2015

Committee Approval Date: September 19, 2024 | **Next Review Date:** 2025

Effective Date: January 1, 2025

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Opdivo (nivolumab) is an intravenously infused immunotherapy [a programmed death receptor-1 (PD-1) inhibitor] that is used in the treatment of several different types of cancers.

Policy/Criteria

Most contracts require pre-authorization approval of Opdivo (nivolumab) prior to coverage.

I. Continuation of therapy (COT): Opdivo (nivolumab) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Opdivo (nivolumab) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) confirming that one of the following criterion A through L below is met.

A. A diagnosis of **urothelial carcinoma** (UC, bladder cancer) in one of the following settings (1, 2, or 3):

1. **Locally advanced (stage III) or metastatic (stage IV), subsequent-line,** when criteria a, b, and c below are met:

a. Disease progression during or following platinum-containing chemotherapy (such as cisplatin or carboplatin).

AND

b. Opdivo (nivolumab) is used as monotherapy.

AND

c. No prior use of a programmed death receptor-1 blocking antibody therapy (PD-1 inhibitor) or programmed death-ligand 1 blocking antibody therapy (PD-L1 inhibitors) [see *Appendix 1*].

OR

2. **Unresectable locally advanced or metastatic, front-line,** when criteria a, b, and c below are met:

a. No prior systemic therapy in the advanced disease setting.

AND

b. Opdivo (nivolumab) will be initiated in combination with cisplatin and gemcitabine.

AND

c. No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

OR

3. **Muscle-invasive urothelial carcinoma** (MIUC) when criteria a through d below are met:

a. The patient has undergone radical resection of the bladder.

AND

b. There is high risk of recurrence as defined by the following (i or ii):

i. Patient received no prior neoadjuvant cisplatin-based chemotherapy: Pathological stage of pT3-pT4a, or pN+.

OR

ii. Patient received prior neoadjuvant cisplatin-based chemotherapy: Pathological stage of ypT2-ypT4a, or ypN+.

AND

c. Opdivo (nivolumab) will be used as an adjuvant monotherapy.

AND

d. No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

OR

B. A diagnosis of **colorectal cancer** (CRC), locally advanced or metastatic, when criteria 1 through 4 below are met:

1. The tumor is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) by immunohistochemistry (IHC) or polymerase chain reaction (PCR) testing.

AND

2. Disease progression during or after standard therapy with a fluoropyrimidine (e.g., fluorouracil, capecitabine), oxaliplatin, AND irinotecan, unless all are not tolerated or there is a documented medical contraindication to all three options.

AND

3. Opdivo (nivolumab) is used as monotherapy or in combination with Yervoy (ipilimumab).

AND

4. No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

OR

C. A diagnosis of **head and neck squamous cell cancer** (HNSCC), recurrent or metastatic, when criteria 1, 2, and 3 below are met:

1. Disease progression on or after a platinum-containing chemotherapy regimen.

AND

2. Opdivo (nivolumab) is used as monotherapy.

AND

3. No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

OR

D. A diagnosis of **hepatocellular carcinoma** (HCC) when criteria 1 through 4 below are met:

1. A documented Child-Pugh score of 5 or 6 (Class A).

AND

2. There has been disease progression on, or intolerance to an HCC-active oral tyrosine kinase inhibitor (TKI) [such as Nexavar (sorafenib) or Lenvima (lenvatinib)].

AND

3. Opdivo (nivolumab) is used in combination with Yervoy (ipilimumab).

AND

4. No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

OR

E. A diagnosis of **classical Hodgkin lymphoma** (CHL) when criteria 1, 2, and 3 are met:

1. Relapse or disease progression in one of the following two settings (a or b):

a. After a hematopoietic stem cell transplant [HSCT; bone marrow transplant (BMT)] and post-transplant Adcetris (brentuximab vedotin).

OR

b. Disease progression on or after three or more lines of therapy that includes an HSCT (BMT).

AND

2. Opdivo (nivolumab) is used as monotherapy.

AND

3. No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

OR

F. A diagnosis of **malignant pleural mesothelioma** (MPM), unresectable, when criteria 1, 2, and 3 below are met:

1. No prior use of systemic therapy for advanced disease.

AND

2. Opdivo (nivolumab) is used in combination with Yervoy (ipilimumab).

AND

3. No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

OR

G. A diagnosis of **melanoma** when either criterion 1 or 2 below is met:

1. Opdivo (nivolumab) is used as monotherapy when either criterion a or b below is met:

a. The patient is diagnosed with **early-stage (IIB or IIC) melanoma** and both of the following criteria are met (i and ii):

i. The tumor is completely resected with negative margins and a negative sentinel lymph node (adjuvant setting).

AND

ii. The patient has had no prior systemic therapy, including no prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

OR

b. The patient is diagnosed with **advanced (stage III or IV) melanoma** and there has been no prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

OR

2. Opdivo (nivolumab) is used in combination with Yervoy (ipilimumab) when criteria a, b, and c below are met:

a. The patient is diagnosed with **advanced (stage III or IV) melanoma**.

AND

b. No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

AND

c. No prior therapy with Yervoy (ipilimumab).

OR

H. A diagnosis of **non-small cell lung cancer** (NSCLC) when criterion 1, 2, or 3 below is met:

1. Earlier-stage, resectable NSCLC, as neoadjuvant therapy, with or without adjuvant therapy, when both criteria (a, b, and c) below are met:

a. Documented stage II, IIIA, or IIIB disease (defined as tumors ≥4 cm and/or node positive)

AND

b. Opdivo (nivolumab) is used as follows (i and ii):

i. For neoadjuvant doses: In combination with platinum-containing chemotherapy in the neoadjuvant setting (prior to surgical resection) for up to four cycles.

AND

ii. If adjuvant therapy is planned: As monotherapy in the adjuvant setting (after surgical resection) for up to 13 cycles.

AND

c. No prior systemic anticancer therapy for NSCLC in any setting, including prior PD-1 inhibitors or PD-L1 inhibitors (see *Appendix 1*).

OR

2. Advanced or metastatic NSCLC, First-line setting, when criteria a, b, and c below are met.

a. Opdivo (nivolumab) is used in combination with Yervoy (ipilimumab) AND one of the following (i or ii) applies:

i. The tumor expresses PD-L1 (≥ 1%).

OR

ii. Given in combination with two cycles of platinum-doublet chemotherapy (regardless of PD-L1 status).

AND

b. No prior systemic therapy for advanced disease.

AND

c. No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

OR

3. Advanced or metastatic NSCLC, Subsequent therapy, when criteria a, b, and c below are met:

a. Opdivo (nivolumab) is used as monotherapy.

AND

b. Disease progression on or after a platinum-containing chemotherapy regimen (such as cisplatin or carboplatin).

AND

c. No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

OR

I. A diagnosis of **renal cell cancer** (RCC), unresectable locally advanced, or metastatic, with clear cell histology and no prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

OR

J. A diagnosis of **squamous cell anal carcinoma** (aSCC), recurrent or metastatic when criteria 1, 2, and 3 below are met:

1. Disease progression on or after cytotoxic chemotherapy.

AND

2. Opdivo (nivolumab) will be used as monotherapy.

AND

3. No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

OR

K. A diagnosis of **esophageal cancer** when one of the following criterion 1, 2, or 3 below is met:

1. A diagnosis of **esophageal squamous cell carcinoma** (ESCC), unresectable advanced or metastatic when either criterion a or b below is met:

a. **First-line setting** when criteria i through v below are met:

i. The patient is not a candidate for surgical resection or definitive chemoradiotherapy (CRT).

AND

ii. Opdivo (nivolumab) will be used in combination with fluoropyrimidine (e.g., fluorouracil, capecitabine)- and platinum (e.g., cisplatin, carboplatin)-containing chemotherapy or ipilimumab (Yervoy).

AND

iii. The tumor expresses PD-L1 (≥ 1%).

AND

iv. No prior systemic therapy in the advanced disease setting.

AND

v. No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

OR

b. **Subsequent-line setting** when criteria i through iii below are met:

i. Disease progression on or after, or intolerance to at least one fluoropyrimidine- and platinum-containing chemotherapy regimen.

AND

ii. Opdivo (nivolumab) is used as monotherapy.

AND

iii. No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

OR

2. A diagnosis of **esophageal adenocarcinoma**, locally advanced or metastatic when criteria a through d below are met:

a. No prior systemic therapy in the advanced disease setting.

AND

b. The tumor is PD-L1 positive as defined by a Combined Positive Score of 5 or more (CPS ≥ 5).

AND

c. Opdivo (nivolumab) will be administered in combination with a fluoropyrimidine (e.g., fluorouracil, capecitabine) and platinum-containing (e.g., cisplatin, oxaliplatin) chemotherapy.

AND

d. No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

OR

3. A diagnosis of **esophageal (adenocarcinoma or ESCC) or gastro-esophageal junction (GEJ) cancer**, stage II or III **resectable**, when criteria a through e below are met:

a. Completion of prior neoadjuvant chemoradiotherapy (must have received both chemotherapy and radiation in neoadjuvant setting).

AND

b. The tumor was completely resected.

AND

c. There is residual pathologic disease (absence of complete pathological response).

PLEASE NOTE: POST OP notes required to establish absence of complete pathological response.

AND

d. Opdivo (nivolumab) will be used as monotherapy.

AND

e. No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

OR

L. A diagnosis of **gastric or gastroesophageal junction (GEJ) cancer**, **locally advanced or metastatic,** when criteria 1 through 4 below are met:

1. No prior systemic therapy in the advanced disease setting.

AND

2. The tumor is PD-L1 positive as defined by a Combined Positive Score of 5 or more (CPS $\geq$ 5).

AND

3. Opdivo (nivolumab) will be administered in combination with a fluoropyrimidine (e.g., fluorouracil, capecitabine) and platinum-containing (e.g., cisplatin, oxaliplatin) chemotherapy.

AND

4. No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Opdivo (nivolumab) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Opdivo (nivolumab) may be authorized as follows (as specified in the coverage criteria above):

Monotherapy or in Combination with chemotherapy:

Diagnosis	Quantity Limit	Total Duration [a]
Neoadjuvant therapy for RESECTABLE cancer (earlier stage NSCLC)	Up to 360 mg every 3 weeks, for up to four doses.	Up to four doses in three months
Adjuvant therapy for RESECTABLE cancer (esophageal cancer, GEJ cancer, muscle-invasive urothelial carcinoma, melanoma, or NSCLC)	Up to 240 mg every 2 weeks (OR 480 mg every 4 weeks)	Up to one year
Other (non-resected): NSCLC, aSCC, advanced melanoma, RCC, UC (bladder cancer), MSI-H/dMMR CRC, classical HL, HNSCC, advanced esophageal, gastric, GEJ cancer	Up to 240 mg every 2 weeks (OR 480 mg every 4 weeks)	Until disease progression

[a] Each authorization will be for up to 24 weeks at a time, or until the course is completed.

Combination therapy with Cabometyx (cabozantinib):

Diagnosis	Quantity Limit	Total Duration [a]
RCC	Up to 240 mg every 2 weeks (OR 480 mg every 4 weeks)	Until disease progression

Combination therapy with Yervoy (ipilimumab):

Diagnosis	Quantity Limit		Total Duration [a]
	Initial, in combination with Yervoy (ipilimumab)	Subsequent, as a monotherapy	
Melanoma	Up to 3 mg/kg every 3 weeks x 4 doses [based on CheckMate 511]	Up to 240 mg every 2 weeks (OR up to 480 mg every 4 weeks)	Until disease progression
HCC	Up to 1 mg/kg every 3 weeks x 4 doses		
CRC (MSI-H/dMMR), RCC	Up to 3 mg/kg every 3 weeks x 4 doses		
ESCC, NSCLC (PD-L1 ≥1)	Up to 3 mg/kg every 2 weeks	Not applicable	Until disease progression, up to 24 months
NSCLC (with 2 cycles platins), MPM	Up to 360 mg every 3 weeks		

[a] Each authorization will be for up to 24 weeks at a time, or until the course is completed.

aSCC: anal squamous cell carcinoma; CRC: colorectal cancer; dMMR: mismatch repair deficient; GEJ: gastro-esophageal junction; HL: Hodgkin lymphoma; HNSCC: head and neck squamous cell cancer; MPM: malignant pleural mesothelioma; MSI-H: microsatellite instability-high; NSCLC: non-small cell lung cancer; RCC: renal cell cancer; UC: urothelial carcinoma

C. Reauthorization: Authorization **shall** be reviewed at least every 24 weeks for documented benefit. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met. Specifically, documentation that the medication is providing clinical benefit, including disease stability or improvement, and lack of disease progression, based on an assessment of change in tumor burden. If there is documentation of potential disease progression, a shortened authorization (up to three months) may be approved to allow time for clarification of response to Opdivo (nivolumab), including clinical re-evaluation of the patient and reimaging.

PLEASE NOTE: Additional doses of Opdivo (nivolumab) will not be authorized without a documented recent assessment by the treating provider (such as oncologist) with objective evidence of response to therapy, such as by re-imaging and use of iRECIST criteria.

IV. The use of Opdivo (nivolumab) in combination with other targeted anti-cancer medications [except with Cabometyx (cabozantinib) for RCC, Yervoy (ipilimumab) for melanoma, CRC, RCC, NSCLC, and HCC, or as specified per the coverage criteria above] is considered investigational.

V. Opdivo (nivolumab) is considered investigational when used for all other conditions, including but not limited to:

- **A.** Glioblastoma multiforme.
- **B.** Microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) tumors [unless specified in the coverage criteria sections above].
- **C.** Multiple myeloma.
- **D.** Ovarian cancer.
- **E.** Small cell lung cancer (SCLC).

Position Statement

- Opdivo (nivolumab) is an intravenously administered human programmed death receptor-1 (PD-1) blocking monoclonal anti-body (immunotherapy) used in the treatment of several types of cancers.
- The intent of this policy is to cover Opdivo (nivolumab) in settings where it has been shown to be safe and effective, as detailed in the coverage criteria, with consideration for other available treatment options.
    * Where there is lack of proven additional benefit and/or lack of demonstrated health outcome (such as overall survival or improved quality of life) relative to alternative therapies, use of Opdivo (nivolumab) alone or in combination with other therapies is not coverable ("not medically necessary" or "investigational").
    * It is important to note that the fact that a medication is FDA approved for a specific indication does not, in itself, make the treatment medically reasonable and necessary.
- Many of the clinical indications for immunotherapies (PD-1, PD-L1, and others) have been approved by the FDA and endorsed by clinical guidelines based on surrogate measures such as overall tumor response rate (ORR) and progression-free survival (PFS) which are not proven to accurately predict clinically important outcomes such as improved overall survival or improved quality of life.
- *PD-L1 expression testing*: is required for coverage of many clinical indications for PD-1 and PD-L1 inhibitors.
    * There are several ways in which PD-L1 expression can be defined. In addition, how PD-L1 expression is defined varies by tumor type and setting.
    * PD-L1 expression is determined by the FDA-approved companion diagnostic testing, based on both the specific PD-1/PD-L1 inhibitor and the tumor type.
    * However, PD-L1 test results are not interchangeable across PD-1/PD-L1 inhibitors and/or indications. There is no conversion available from one type of test to another, such as combined positive score (CPS) versus tumor proportion score (TPS) versus percent of tumor cells (TC). Therefore, the correct test must be conducted for proper selection of patient populations for a given use.
- National Comprehensive Cancer Network (NCCN) guidelines recommend Opdivo (nivolumab) as a potential option in each of the treatment settings listed in the coverage criteria. In general, NCCN recommendations parallel the FDA approved indications.
- The PD-1 and PD-L1 inhibitors have the potential to cause immune-mediated adverse reactions that can result in pneumonitis, colitis, hepatitis, endocrinopathies, and nephritis.
- Opdivo (nivolumab) is coverable in doses and quantities up to those specified in the coverage criteria, until disease progression or unacceptable toxicity.
- Optimal sequencing of chemotherapy and immunotherapy in many cancers is unknown or the data is evolving. At this time, sequential use of immunotherapies is not supported by current evidence. Specifically, there is no evidence to support the sequential use of different PD-1 or PD-L1 inhibitors once there is disease progression on prior PD-1 or PD-L1 inhibitor therapy, as well as use of adjuvant PD-1/PD-L1 inhibitor after neoadjuvant PD-1/PD-L1 inhibitor therapy (unless explicitly listed in the coverage criteria). Therefore, the use of sequential courses of PD-1/PD-L1 immunotherapy is not coverable.

- Although there is interest in the use of Opdivo (nivolumab) / Yervoy (ipilimumab), a combination immunotherapy, after progression on other therapies, Opdivo (nivolumab) / Yervoy (ipilimumab) is only coverable in the settings in which it was studied and NOT as a salvage therapy. In addition, the use of Opdivo (nivolumab) / Yervoy (ipilimumab) after progression on a monotherapy PD-1/PD-L1 inhibitor therapy [e.g., Keytruda (pembrolizumab)] is also not coverable.
- There are ongoing studies using Opdivo (nivolumab) in a variety of other cancers. However, although initial evidence may be promising, the potential for clinical benefit in these conditions is still being investigated.
- The use of Opdivo (nivolumab) for small cell lung cancer (SCLC), as well as a monotherapy in HCC, is now considered investigational. The FDA indications for SCLC and HCC (monotherapy) were withdrawn after confirmatory trials failed to demonstrate an improvement in any health outcome when used in these settings.
- *Reauthorization Criteria*: When coverage criteria are met, Opdivo (nivolumab) is authorized for six months (24 weeks) of therapy, after which time documentation must be provided to establish that the medication is effective. Specifically, there must be documentation of clinical benefit, including disease stability or improvement and there is a lack of disease progression, based on an assessment of change in tumor burden. Documentation of benefit must include an assessment of the most recent imaging ("restaging scans") and/or re-biopsy by the treating oncologist.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy

UROTHELIAL CARCINOMA (BLADDER CANCER)

- Advanced (locally advanced or metastatic) UC, subsequent-line setting: Opdivo (nivolumab) received FDA Accelerated approval for unresectable or metastatic bladder cancer based on a single-arm, observational trial that evaluated tumor objective response rates (ORR) [CHECKMATE-275]. [1,2] Clinical benefit has not been established.
  * Subjects had disease that progressed during or following a platinum-containing chemotherapy regimen, or progressive disease within 12 months of treatment with a platinum-containing chemotherapy regimen administered in the adjuvant (after surgical resection) or neoadjuvant (prior to surgical resection) settings.
  * ORR was 19.6%, of which the vast majority (17%) were partial responders.
  * ORR has not been shown to accurately predict clinically relevant outcomes. Additional confirmatory studies are needed to establish a clinical benefit.
- Advanced (unresectable locally advanced or metastatic) UC, first-line setting: Opdivo (nivolumab) received FDA approval as a first-line therapy for unresectable locally advanced or metastatic bladder cancer when initiated in combination with cisplatin plus gemcitabine and then continued as monotherapy. Approval was based on a randomized, open-label trial [CheckMate-901] that compared this combination with cisplatin plus gemcitabine alone. [3]
  * Subjects were previously untreated in the advanced treatment setting; however, prior neoadjuvant or adjuvant chemotherapy was allowed as long as recurrence took place 12 or more months after completion of therapy. Patients who were not eligible for cisplatin-based chemotherapy were excluded from the study.
  * Opdivo (nivolumab) was initiated in combination with cisplatin plus gemcitabine which were given for up to six cycles, after which Opdivo (nivolumab) was continued every four weeks as monotherapy until disease progression, or for up to two years maximum from the first dose.
  * The study demonstrated a survival advantage with median OS of 21.7 months and 18.9 months in the Opdivo (nivolumab) and chemotherapy only treatment arms, respectively (HR 0.78 [95% CI: 0.63, 0.96]; p-value = 0.017).
- Adjuvant therapy for early-stage MIUC: Opdivo (nivolumab) received FDA approval as an adjuvant therapy (after complete surgical resection) for patients with early-stage muscle-invasive urothelial carcinoma (MIUC) [also known as muscle-invasive bladder cancer (MIBC)] with good performance status and a high risk of disease recurrence. Approval was based on a randomized, double-blind, placebo-controlled trial [CHECKMATE-274] that evaluated disease-free survival (DFS) as the primary endpoint. [4]
  * The population was primarily White, male, and with a median age of 66 years (generally younger than a typical patient which has a median age of 73 years at diagnosis). Forty percent had a PD-L1 $\geq$ 1%.
  * Approximately 80% of patients had tumors originating in the bladder, with the remaining 20% originating in the renal pelvis or ureter.
  * Approximately 44% of subjects had prior neoadjuvant cisplatin-based chemotherapy.

    * The DFS was 20.8 months and 10.8 months in the Opdivo (nivolumab) and placebo arms, respectively (HR 0.70; [95% CI: 0.57, 0.86]; p = 0.0008).
    * DFS has not been shown to accurately predict improvement in any clinically relevant outcome in early-stage MIUC. It is not known if adjuvant therapy will ultimately improve overall survival (OS), the outcome of interest. In addition, the ideal sequencing of agents in this clinical setting has not been determined.

- The NCCN guideline lists Opdivo (nivolumab) monotherapy for UC as follows: [5]
    * ***Locally advanced or metastatic disease:*** Opdivo (nivolumab) and Opdivo (nivolumab)-based regimens are listed among several first- and subsequent-line therapy recommendations.
    * ***Adjuvant therapy for newly diagnosed MIUC with a high risk of recurrence:*** Listed among potential therapy options.

COLORECTAL CANCER (CRC), MSI-H/dMMR

- Opdivo (nivolumab) received FDA Accelerated approval for progressive MSI-H/dMMR metastatic CRC based on tumor response from an uncontrolled, single-arm (observational) study in cohort of subjects (N = 53) whose disease had progressed during or after treatment with all standard options: fluoropyrimidine, oxaliplatin, and irinotecan [CHECKMATE-142]. [2,6] To date, there is no evidence that it provides any clinical benefit in this setting.
    * ORR was 28% (1.9% were considered to have a complete tumor response).
    * PD-L1 expression was not a condition for enrollment in the trial.
    * ORR has not been shown to accurately predict clinically relevant outcomes. Additional confirmatory studies are needed to establish a clinical benefit.
- Opdivo (nivolumab) monotherapy is listed among the treatment options for MSI-H/dMMR CRC after progression on fluoropyrimidine, oxaliplatin, and irinotecan. [5]

HEAD AND NECK SQUAMOUS CELL CANCER (HNSCC)

- Opdivo (nivolumab) received approval for recurrent or metastatic HNSCC based on improved overall survival (OS), a clinically relevant endpoint, relative to investigator's choice of Erbitux (cetuximab) or single-agent chemotherapy in an open-label randomized controlled trial (N = 361) [CHECKMATE-141]. [2,7]
    * The trial included cancer of the oral cavity, pharynx, or larynx that was not amenable to curative therapy and progressive disease within 6 months of receiving platinum-based chemotherapy.
    * Median OS was 7.5 months and 5.1 months in the Opdivo (nivolumab) and investigator's choice of therapy treatment arms, respectively. A subgroup analysis demonstrated greater improvement in median OS with Opdivo (nivolumab) when at least 1% of the cells in the tumor expressed PD-L1 (tumor proportion score of > 1%).
- The NCCN guidelines list Opdivo (nivolumab) monotherapy among treatment options for non-nasopharyngeal HNSCC when there has been disease progression on or after platinum-containing chemotherapy. [5]

HEPATOCELLULAR CARCINOMA (HCC)

- Opdivo (nivolumab) received FDA Accelerated approval for use in HCC after progression of disease on, or intolerance to, Nexavar (sorafenib) when given in combination with Yervoy (ipilimumab) based on a small, single-arm, preliminary study [CHECKMATE-040] that evaluated tumor response rate. Clinical benefit in this setting has not been demonstrated. [2,8]
    * Subjects had progressive disease while on, or had intolerance to, Nexavar (sorafenib) therapy.
    * Patients had Child-Pugh Class A disease (a score of A5 in 82%, and A6 in 18% of patients) and 80% had disease that had spread beyond the liver.
    * An ORRs of 33% was reported with this regimen. ORR has not been shown to accurately predict clinically relevant outcomes. Additionally, it is not known how Opdivo (nivolumab) plus Yervoy (ipilimumab) compares with other second-line HCC therapies.
- The Accelerated FDA indication for use of Opdivo (nivolumab) as a monotherapy in HCC after progression of disease on, or intolerance to, Nexavar (sorafenib) was withdrawn by the manufacturer in July of 2021 because clinical benefit was not demonstrated in confirmatory trials.
- The NCCN guideline lists Opdivo (nivolumab) monotherapy, or in combination with Yervoy (ipilimumab), among treatment options for progressive of disease after Nexavar (sorafenib) and the patient is Child-Pugh Class A (or B7 for monotherapy). [5]

CLASSICAL HODGKIN LYMPHOMA (CHL)

- Opdivo (nivolumab) received FDA Accelerated approval for as a monotherapy relapsed or refractory CHL based on two, small, single-arm, trials that measured tumor response rate [CHECKMATE-205 and -039]. Clinical benefit in this setting has not been established. [2,9]
    * Subjects had relapsed or refractory disease and had prior high-dose chemotherapy followed by autologous stem cell transplant rescue, and post-transplantation Adcetris (brentuximab vedotin). The median number of prior systemic regimens was four. *[Note: PD-1 inhibitors, such as Opdivo (nivolumab), should NOT be given after an allogeneic stem cell transplant as it may cause serious and potentially fatal immunologic reactions].*
    * ORR, the primary endpoint, not been shown to correlate with clinical outcomes such as improved symptom control, function, or quality of life, or prolonged OS.
- The NCCN guideline lists Opdivo (nivolumab) among several single-agent treatment options for relapsed or refractory CHL after high-dose chemotherapy with autologous stem cell rescue and Adcetris (brentuximab vedotin). [5]
- There is interest in the use of Opdivo (nivolumab) in combination with Adcetris (brentuximab vedotin) for cHL. However, there is insufficient evidence at this time to establish the safety or efficacy of this combination. The evidence for use in the relapsed/refractory setting is limited to phase 1 and 2 trial interim data. [10,11] Additional trials are ongoing. In the front-line setting in chemotherapy-ineligible patients, the primary endpoint (ORR) was not met with the use of Opdivo (nivolumab) in combination with Adcetris (brentuximab vedotin). [12]

MALIGNANT MELANOMA

First-line Advanced Melanoma Setting

- The primary evidence of efficacy for Opdivo (nivolumab) in previously untreated (first-line setting) patients with unresectable (stage IIIB) or metastatic (stage IV) melanoma is based on a phase 3, double-blind randomized controlled trial that compared Opdivo (nivolumab) monotherapy with dacarbazine [CHECKMATE-066]. [2,13]
    * All enrolled subjects were without a BRAF mutation.
    * Progression-free survival (PFS), a secondary endpoint, was 5.1 months with Opdivo (nivolumab) and 2.2 months with dacarbazine.
    * Preliminary survival rates at 1 year were 72.9% and 42.1% with Opdivo (nivolumab) and dacarbazine, respectively. In a subsequent three-year analysis, median OS was substantially longer in the Opdivo (nivolumab) group in a subsequent analysis. [14]

First-line Advanced Melanoma Setting in Combination with Yervoy (ipilimumab)

- The efficacy of Opdivo (nivolumab) when administered in combination with Yervoy (ipilimumab) for unresectable or metastatic melanoma in the first-line setting is based two RCTs, which found improved PFS relative to monotherapy with either drug alone. OS data was not yet mature at the time these trials were published. [2,15]
- A follow-on study (CheckMate 511) was conducted to determine whether adjustments in the dosing of Opdivo (nivolumab) and Yervoy (ipilimumab) might improve the tolerability of the combination. The currently approved dose is Opdivo (nivolumab) 1 mg/kg plus Yervoy (ipilimumab) 3 mg/kg IV every 3 weeks for 4 doses. The study found that Opdivo (nivolumab) 3 mg/kg plus Yervoy (ipilimumab) 1 mg/kg IV every 3 weeks for 4 doses was better tolerated without negatively impacting tumor response rate after a minimum of 12 months follow up. The median OS was not reached in either group. [16]

Opdivo (nivolumab) as Subsequent Therapy for Advanced Melanoma

- Opdivo (nivolumab) has also been evaluated in patients with advanced melanoma whose disease was refractory to therapy with Yervoy (ipilimumab) and, if BRAF mutation positive, BRAF inhibitor therapy. [17,18]
    * Efficacy was based on improved tumor response rates relative to chemotherapy. There was no information with regard to improvement in any clinically relevant outcome in this setting at the time these trials were published.
    * Confirmatory evidence of efficacy in this melanoma setting was not yet mature at the time the trial was published.

Opdivo (nivolumab) as an Adjuvant Therapy for Resectable Melanoma

- Opdivo (nivolumab) was evaluated as an adjuvant therapy in patients with resectable stage IIIB/C or stage IV (metastatic) melanoma after complete surgical resection, as compared to Yervoy (ipilimumab) [CHECKMATE-238]. [19]
    * Treatment was started within 12 weeks of tumor resection and was continued for up to one year.
    * There was a statistically significant improvement in recurrence-free survival (RFS) with Opdivo (nivolumab) relative to Yervoy (ipilimumab). However, improvement in OS, a clinically relevant endpoint, is unknown.

- Opdivo (nivolumab) was evaluated as an adjuvant therapy in patients with early-stage (IIB/C) after complete surgical resection (negative margins and negative sentinel lymph node) where it was compared with placebo (best supportive care) [CHECKMATE-76K]. [20]
    * Patients in the study were naïve to prior systemic therapy and treatment with Opdivo (nivolumab) was started within 12 weeks of tumor resection and was continued for up to one year.
    * There was a statistically significant improvement in recurrence-free survival (RFS) with Opdivo (nivolumab) relative to Yervoy (ipilimumab). However, improvement in OS, a clinically relevant endpoint, is unknown.
- The NCCN guideline lists Opdivo (nivolumab), as monotherapy or in combination with Yervoy (ipilimumab), among treatment options for metastatic or unresectable for *BRAF V600* wild-type melanoma. Opdivo (nivolumab) is also listed for second-line or subsequent therapy when used as a monotherapy as well as when used in the adjuvant setting for resected stage IIB/C, IIIB/C and stage IV disease. [5]

MALIGNANT PLEURAL MESOTHELIOMA (MPM)

The efficacy of Opdivo (nivolumab) in combination with Yervoy (ipilimumab) for unresectable MPM in the first-line setting is based on one randomized, open-label trial, which found improved OS relative to chemotherapy (platinum plus pemetrexed) alone (18.1 vs. 14.1 months) [CHECKMATE-743]. [21]

- The NCCN guideline for MPM lists both platinum-based chemotherapy [category 1] and nivolumab plus ipilimumab [category 2A] as first-line, preferred regimens. Nivolumab with or without ipilimumab (if not used in 1st-line) is also listed as a second-line, treatment option [category 2A]. However, there are no trials for the use of nivolumab with or without ipilimumab as a second-line therapy. Therefore, the use of nivolumab in the 2nd line setting is not coverable. [5]

NON-SMALL LUNG CANCER (NSCLC)

RESECTABLE DISEASE (EARLY NSCLC)

Neoadjuvant (prior to surgical resection) for earlier NSCLC:

- The efficacy of Opdivo (nivolumab) as a neoadjuvant therapy for resectable NSCLC was evaluated in an open-label randomized controlled trial that evaluated event-free survival (EFS) and pathological complete response (pCR) as surrogate endpoints. The trial compared the addition of Opdivo (nivolumab) to a platinum doublet with the platinum doublet alone. Therapy was given prior to surgical resection every three weeks for a total of 3 doses. [22]
    * Patients enrolled in the trial had resectable disease with tumors ≥ 4 cm and/or positive nodes.
    * Approximately 50% of the population had PD-L1 expression ≥ 1%.
    * The median EFS was 31.6 months and 20.8 months in the Opdivo (nivolumab)/platinum doublet and platinum doublet treatment arms, respectively [HR 0.63 (97.5% CI: 0.43, 0.91); p=0.005).
    * The rate of pCR was 24% and 2.2% in the Opdivo (nivolumab)/platinum doublet and platinum doublet treatment arms, respectively.
    * Data for overall survival (OS) were not mature in either treatment arm.

- Limitations of the study include the use of surrogate endpoints which do not accurately reflect relevant clinical outcomes, and potential undertreatment of patients in the comparator arm as standard of care neoadjuvant therapy in this setting is generally four doses of platinum doublet therapy.

Neoadjuvant therapy followed by adjuvant therapy for earlier NSCLC:

- An RCT [CHECKMATE 77T] evaluated Opdivo (nivolumab) in resectable NSCLC as an add-on to platinum-containing chemotherapy used in the neoadjuvant setting (prior to surgical resection), and then continued as a monotherapy in the adjuvant setting (after surgical resection).[23]
    * Patients had pathologically confirmed stage II, IIIA, or IIIB NSCLC [involvement of >1 ipsilateral mediastinal lymph node or subcarinal lymph node (N2 stage)], no EGFR mutations or known ALK translocations, and no prior systemic anticancer treatment.
    * Placebo or Opdivo (nivolumab) was given 360 mg every three weeks for 4 cycles (4 doses) prior to surgical resection, and then placebo or Opdivo (nivolumab) 480 mg every 4 weeks was continued until disease progression or up to a maximum of one year [up to 13 cycles (13 doses, as 360 mg every 4 weeks)] after surgical resection. All patients received neoadjuvant platinum-doublet chemotherapy every 3 weeks for 4 cycles.
    * The primary endpoint was event-free survival (EFS). The median EFS was not reached in the Opdivo (nivolumab) treatment arm and was 18.4 months in the placebo arm with a hazard ratio of 0.58 [97.63% CI: 0.42, 0.81] and p-value <0.001. OS results are not mature; however, no difference in OS has been detected to date.
- EFS is not a validated surrogate endpoint. It has not been shown to accurately predict significant improvement in clinical endpoints of interest such as OS and quality of life.
- The NCCN NSCLC guideline lists neoadjuvant therapy with Opdivo (nivolumab) among treatment options for resectable NSCLC (three cycles total). Platinum doublet therapy is also an option (four cycles total), as are various adjuvant therapies. [24]

METASTATIC DISEASE (mNSCLC)

Front-line use:

In Combination with Yervoy (ipilimumab) and Platinum-Doublet for mNSCLC

- The efficacy of Opdivo (nivolumab) when administered in combination with Yervoy (ipilimumab) and two cycles of platinum-doublet chemotherapy for recurrent or metastatic NSCLC in the first-line setting is based on one randomized, open-label trial, which found improved OS relative to chemotherapy alone [CHECKMATE-9LA]. [18]
    * Subjects received Opdivo (nivolumab) 360 mg IV every 3 weeks, Yervoy (ipilimumab) 1 mg/kg IV every 6 weeks, and platinum-doublet chemotherapy IV every 3 weeks for 2 cycles; or platinum-doublet chemotherapy administered every 3 weeks for 4 cycles. Study treatment continued until disease progression, unacceptable toxicity, or for up to 2 years.

* Patients received no prior systemic therapy for metastatic disease.
* OS was 14.1 months with the addition of nivolumab/ipilimumab versus 10.7 months with chemotherapy alone. These efficacy results are from the prespecified interim analysis when 351 events were observed (87% of the planned number of events for final analysis). With an additional 4.6 months of follow-up, the hazard ratio for overall survival was 0.66 (95% CI: 0.55, 0.80) and median survival was 15.6 months (95% CI: 13.9, 20.0) and 10.9 months (95% CI: 9.5, 12.5) for patients in the treatment arm or control arm, respectively.

In Combination with Yervoy (ipilimumab) for mNSCLC

- The efficacy Opdivo (nivolumab) with Yervoy (ipilimumab) for metastatic NSCLC in the first-line setting is based on one open-label, phase 3 trial, which found improved OS versus chemotherapy in PD-L1 expressing tumors [CHECKMATE-227]. [25]
  * Patients had received no prior systemic therapy for metastatic disease.
  * Among the patients with a PD-L1 expression level of 1% or more, the median OS was 17.1 months with nivolumab plus ipilimumab vs. 14.9 months with chemotherapy, with 2-year overall survival rates of 40.0% and 32.8%, respectively.

Monotherapy for mNSCLC:

- Front-line treatment of metastatic NSCLC with single agent Opdivo (nivolumab) was not superior to chemotherapy based on a phase 3 trial in this setting. The study failed to meet its primary endpoint of PFS [KEYNOTE-026]. [26] No information on OS has been released to date.

Subsequent-line use:

Opdivo (nivolumab) as Subsequent Therapy for Metastatic NSCLC

- The efficacy of Opdivo (nivolumab) in metastatic NSCLC is based on two RCTs, one in subjects with squamous histology and one in subjects with nonsquamous histology. [2,27,28]
  * Subjects enrolled in the trials had progression of disease during or after chemotherapy with a platinum doublet. Patients with a known EGFR mutation or ALK translocation were allowed to have one additional line of tyrosine kinase inhibitor therapy. The studies compared Opdivo (nivolumab) 3 mg/kg IV every two weeks with docetaxel 75 mg/m^2 IV every three weeks. Both were administered as monotherapy.
  * Median OS was statistically superior in the Opdivo (nivolumab) treatment arm relative to the docetaxel arm in both squamous and nonsquamous populations. The difference was considered to be clinically relevant.
  * In the population with nonsquamous histology, it was noted that there was a positive correlation between the level of PD-L1 expression and the efficacy of Opdivo (nivolumab) in metastatic NSCLC. Although Opdivo (nivolumab) therapy is currently not selected based on level of PD-L1 expression, future studies may help to clarify the role of testing in the selection of patients who are most likely to benefit from this therapy.
  * The clinical utility of nivolumab as a first-line therapy in NSCLC (nonsquamous or squamous) has not been demonstrated.

- The NCCN guideline lists Opdivo (nivolumab) monotherapy among recommended treatment options for locally advanced or metastatic squamous and nonsquamous NSCLC when used as a subsequent therapy. [5]

RENAL CELL CARCINOMA (RCC)

Front-line use:

In Combination with Yervoy (ipilimumab)

- A large, randomized, open-label trial compared the combination of Yervoy (ipilimumab) plus Opdivo (nivolumab) with Sutent (sunitinib) as initial therapy for patients with intermediate- to poor risk, unresectable or metastatic RCC [CHECKMATE-214]. [29]
  * Yervoy (ipilimumab) was initiated for four doses with Opdivo (nivolumab) then Opdivo (nivolumab) monotherapy was continued until disease progression.
  * The population included favorable-, intermediate-, or poor-risk disease; however, only patients with intermediate- or poor risk disease were evaluated for efficacy.
  * There was no statistical difference in PFS between the two treatment groups. Efficacy was based on a modest improvement in survival at 18 months (interim analysis) relative to Sutent (sunitinib). Median survival has not been reached in either group. It is too soon to make conclusions regarding its net health benefit in this setting.
- The NCCN guideline lists Opdivo (nivolumab) among the recommended front-line therapies for patients with intermediate- to poor risk advanced RCC when given in combination with Yervoy (ipilimumab). [5]

In Combination with Cabometyx (cabozantinib)

- A large, open-label, randomized active-controlled trial compared the combination of Opdivo (nivolumab) plus cabozantinib with Sutent (sunitinib) in treatment-naïve patients with locally advanced (unresectable) or metastatic RCC with clear cell histology [CHECKMATE-9ER]. [18]
  * Patients were enrolled regardless of tumor PD-L1 expression.
  * The population included patients with favorable-, intermediate-, and poor-risk disease; however, approximately 75% had intermediate- to poor-risk disease.
  * The median PFS was 16.6 months and 8.3 months in the Opdivo (nivolumab)/Cabometyx (cabozantinib) and Sutent (sunitinib) treatment groups, respectively.
  * Median OS was not reached in either group; however, early results favor the Opdivo (nivolumab)/Cabometyx (cabozantinib) treatment arm.
- A more informative comparator would have been a monotherapy Cabometyx (cabozantinib) arm.
- The NCCN guideline lists the combination of Opdivo (nivolumab) and Cabometyx (cabozantinib) among several front-line options for advanced RCC with clear cell histology.[5]

In combination with Yervoy (ipilimumab) and Cabometyx (cabozantinib)

- A large, phase 3, RCT [COSMIC-313] compared the combination of Opdivo (nivolumab)/ Yervoy (ipilimumab)/Cabometyx (cabozantinib) with Opdivo (nivolumab)/Yervoy (ipilimumab)/placebo in patients with intermediate- to poor-risk advanced or metastatic RCC with a clear cell component. An incremental improvement in PFS was noted in the 'triple therapy' group; however, there is no mature outcomes data from the study. [30]
- The risk of significant AEs was greater in the Opdivo (nivolumab)/Yervoy(ipilimumab)/ Cabometyx (cabozantinib) treatment arm with grade 3 or 4 AEs occurring in 79% of the patients in the 'triple therapy group' versus 56% in the control group.
- It is not known how Opdivo (nivolumab)/Yervoy (ipilimumab)/Cabometyx (cabozantinib) compares with Opdivo (nivolumab)/Cabometyx (cabozantinib) which is already FDA approved and coverable in this population.
- The NCCN guideline does not endorse the use of Opdivo (nivolumab)/Yervoy (ipilimumab)/Cabometyx (cabozantinib) for RCC. [24,31]

Subsequent-line use:

- The primary evidence of efficacy in RCC is based on a phase 3, double-blind randomized controlled trial that compared Opdivo (nivolumab) monotherapy with Afinitor (everolimus) in patients with refractory unresectable or metastatic RCC, after prior antiangiogenic therapy with bevacizumab or a multi-kinase inhibitor. [2,32]
    * Subjects were previously treated with at least one of the following: bevacizumab, Sutent (sunitinib), Votrient (pazopanib), Inlyta (axitinib), or Nexavar (sorafenib).
    * Efficacy was based on improved OS with Opdivo (nivolumab), a clinically relevant endpoint, relative to Afinitor (everolimus) at the time of the prespecified interim analysis (median OS of 25 months and 19.6 months, respectively).
- The NCCN guideline lists Opdivo (nivolumab) among several treatment options for subsequent therapy of unresectable or metastatic RCC after progression of disease on front-line therapy [e.g. multi-kinase inhibitors, bevacizumab]. [5]

GASTRIC, GASTROESOPHAGEAL JUNCTION (GEJ), AND ESOPHAGEAL ADENOCARCINOMA CANCER - ADVANCED

- The efficacy of Opdivo (nivolumab) in gastric, GEJ, and advanced esophageal cancer is based on a phase 3, open-label, randomized controlled trial [CheckMate-649] that compared front-line treatment with Opdivo (nivolumab) plus chemotherapy versus chemotherapy alone in patients with unresectable advanced, or metastatic gastric or GEJ cancer and esophageal adenocarcinoma. [2,33]
    * Seventy percent of the population had gastric cancer, 18% had GEJ cancer, and the remaining 12% had esophageal adenocarcinoma. Ninety-six percent of the population had metastatic disease.
    * Opdivo (nivolumab) was given in combination with fluoropyrimidine (fluorouracil or capecitabine) plus oxaliplatin chemotherapy. Patients in the comparator arm received the same chemotherapy regimen given alone.

    * The trial initially enrolled patients regardless of PD-L1 CPS status; however, a protocol amendment was made when the trial was underway which required a PD-L1 CPS of 5% or more. This resulted in an overall population of patients with tumors that had a higher-than-average PD-L1 CPS expression (the population was enriched with high PD-L1-expressing tumors).
    * Efficacy was based on the primary efficacy population of patients with tumors with a PD-L1 CPS $\geq$ 5. The median OS was 14.4 months and 11.1 months in the Opdivo (nivolumab) and comparator arms, respectively.
    * Results in the ITT population (all patients, regardless of tumor PD-L1 CPS expression) are not reliable as this population was enriched with patients whose tumors had high PD-L1 CPS expression and were more likely to respond to PD-1 inhibitor therapy.
- The NCCN guideline lists Opdivo (nivolumab) when used in combination with a fluoropyrimidine plus oxaliplatin among several treatment options for the front-line treatment of unresectable locally advanced or metastatic gastric or GEJ cancer, as well as esophageal or esophagogastric junction adenocarcinoma, with a PD-L1 combined positive score (CPS) of at least 5. [5]

ESOPHAGEAL AND GASTROESOPHAGEAL JUNCTION (GEJ) CANCER

Early-Stage (Resectable) Esophageal or GEJ Cancer – as ADJUVANT therapy

- The efficacy of Opdivo (nivolumab) in esophageal or GEJ cancer is based on a phase 3, randomized, double-blind controlled trial [CheckMate-577] that compared adjuvant treatment with Opdivo (nivolumab) versus placebo in patients with stage II or III (resectable) esophageal or GEJ. [2,34]
    * The trial included tumors with both adenocarcinoma (71%) and squamous cell carcinoma (29%) histology.
    * All patients had to have completed neoadjuvant chemoradiotherapy (CRT) followed by a complete resection where the patient was rendered free of disease.
    * Additionally, all patients had residual pathological disease (absence of pathological complete response) after their initial treatment. Patients with resectable metastatic disease were not eligible to participate in the study.
    * Patients were randomized to either nivolumab or placebo for a total duration of up to one year of adjuvant therapy.
    * Efficacy was based on disease-free survival, an unvalidated surrogate endpoint. Median DFS was 22.4 months and 11.0 months in the Opdivo (nivolumab) and placebo treatment arms, respectively. OS results are not mature.
- NCCN guideline lists Opdivo (nivolumab) among several treatment options for adjuvant use in resected esophageal or esophagogastric junction cancer with residual disease. [5]

Advanced Esophageal Squamous Cell Cancer (ESCC)

- The efficacy of Opdivo (nivolumab) in refractory, unresectable advanced, recurrent, or metastatic ESCC is based on a phase 3, open label, randomized controlled trial that compared Opdivo (nivolumab) with investigator's choice of taxane (paclitaxel or docetaxel). There was a modest OS improvement with Opdivo (nivolumab) relative to chemotherapy [ATTRACTION-3]. [35]

* Patients were refractory or intolerant to at least one fluoropyrimidine- and platinum-based regimen.
* At a minimum follow-up time (i.e., time from random assignment of the last patient to data cutoff) of 17.6 months, OS was statistically significantly improved with Opdivo (nivolumab) versus chemotherapy (median 10.9 *vs* 8.4 months).

- Opdivo (nivolumab) was also approved as a potential front-line therapy in combination with fluoropyrimidine- and platin-based chemotherapy or ipilimumab for unresectable advanced or metastatic ESCC based on a large randomized, open-label trial that demonstrated a 2- to 2.5-month improvement in median OS relative to chemotherapy alone. [36] This is likely an overestimate of expected survival benefit in the general population due to the following:
  * The trial was enriched with patients whose tumors overexpressed PD-L1 (PD-L1 ≥ 1%) and were therefore more likely to respond to this immunotherapy combination. Subgroup analyses support this analysis as there was a 6-month improvement in median OS relative to standard chemotherapy in the PD-L1 ≥ 1% population; however, there was no survival benefit relative to chemotherapy in the PD-L1 < 1% population. *(Note: 49% of the study population had PD-L1 expression ≥ 1%)*
  * Only 16% of patients in the chemotherapy arm received a PD-(L)1 inhibitor after disease progression. Follow-on therapy with a PD-(L)1 inhibitor is standard of care in the US based on current guidelines. There are currently two PD-1 inhibitors approved as monotherapy for ESCC in the second-line setting (after progression on chemotherapy).
- Optimal sequencing of therapies in esophageal carcinomas has not yet been determined.
- The NCCN guideline lists Opdivo (nivolumab) as a potential treatment option in the following advanced ESCC settings: [5]
  * ***Front-line:***
    - In combination with ipilimumab [category 2A]
    - Although the FDA approved the use of Opdivo (nivolumab) in combination with chemotherapy as a front-line therapy for ESCC, it is not routinely recommended in the guideline [category 2B].
  * ***Second-line:*** As monotherapy [category 1] among several treatment options for second- or subsequent-line therapy of advanced ESCC.

Advanced Esophageal Adenocarcinoma

- The efficacy of Opdivo (nivolumab) in advanced esophageal adenocarcinoma is based on a phase 3, open-label, randomized controlled trial [CheckMate-649] that compared front-line treatment with Opdivo (nivolumab) plus chemotherapy versus chemotherapy alone in patients with unresectable advanced, or metastatic gastric or GEJ cancer, or esophageal adenocarcinoma. [2,33]

  Note: This same trial was used for the approval of Opdivo (nivolumab) in advanced gastric and GEJ cancer. (See "GASTRIC, AND GASTROESOPHAGEAL JUNCTION (GEJ), AND ESOPHAGEAL ADENOCARCINOMA CANCER - ADVANCED") [5]

ANAL SQUAMOUS CELL CARCINOMA (aSCC)

- Although not FDA-approved for this use, Opdivo (nivolumab) and Keytruda (pembrolizumab) have been used in anal squamous cell carcinoma that is refractory to or recurs on front-line chemotherapy due to the lack of other effective therapies.
- The majority of patients with aSCC respond well to standard cytotoxic chemotherapy.
- Preliminary studies suggest these therapies have potential activity in this setting:
  * There was a reported ORR of 17% (all partial responses) in 24 patients with recurrent PD-L1-positive (> 1%) advanced anal squamous cell carcinoma who received Keytruda (pembrolizumab). [37]
  * There was a reported ORR of 24% (two complete and seven partial responses) in 37 patients with treatment refractory metastatic anal squamous cell carcinoma who received Opdivo (nivolumab). [38]
  * Additional studies are needed to establish whether there is a lasting clinical benefit with these PD-1 inhibitors in this treatment setting.
- Both Keytruda (pembrolizumab) and Opdivo (nivolumab) are listed as treatment options as subsequent therapy for recurrent anal carcinoma in the NCCN guideline. [5]
- Given the lack of treatment alternatives in a relatively small patient population, the use of Opdivo (nivolumab) is considered medically necessary and coverable in chemotherapy-refractory disease.

INVESTIGATIONAL USES

- *Small cell lung cancer (SCLC)*:
  * Opdivo (nivolumab) received Accelerated approval for in metastatic SCLC, based on a small, single-arm, open label study that evaluated tumor response rate in a cohort of patients with pretreated metastatic SCLC [CHECKMATE-032]. [39]
  * However, subsequent trials [CHECKMATE -451 and -331) failed to demonstrate a proven health benefit and the company withdrew the FDA indication. [40] Therefore, the use of Opdivo (nivolumab) for SCLC is considered investigational at this time.
- *Hepatocellular carcinoma (HCC):* A confirmatory phase 3 trial (CheckMate 459) comparing Opdivo (nivolumab) with Nexavar (sorafenib) as a front-line therapy for advanced HCC failed to show any overall survival advantage with Opdivo (nivolumab). Coverage is only provided for Opdivo (nivolumab) when it is given in combination with Yervoy (ipilimumab). [41]
- *Glioblastoma:* An open-label, phase 3 study [NCT02617589] compared Opdivo (nivolumab) plus radiotherapy with temozolomide plus radiotherapy in patients with newly diagnosed glioblastoma multiforme. Temozolomide plus radiotherapy, the standard of care, demonstrated superior overall survival relative to Opdivo (nivolumab) plus radiotherapy. [42]
- *Melanoma, adjuvant Opdivo (nivolumab) plus Yervoy (ipilimumab):* A phase 3, double-blind RCT [CheckMate 915] compared Opdivo (nivolumab) plus Yervoy (ipilimumab) with Opdivo (nivolumab) plus placebo as an adjuvant therapy for up to one year after resection (with no evidence of residual disease) of their stage IIIB-D or IV cutaneous melanoma. The trial found that the addition of Yervoy (ipilimumab) to adjuvant Opdivo (nivolumab) did not improve relapse-free survival rates; however, the risk of grade 3 or 4 adverse effects (AEs) and discontinuation of therapy due to AEs was greater. [43]

- *Other cancers*: PD-1 inhibitor medications, including Opdivo (nivolumab), are actively being studied in many different cancers. Ongoing areas of research include, but are not limited to, use in multiple myeloma, ovarian cancer, and DLBCL (other than listed in the coverage criteria). [44,45] Whether Opdivo (nivolumab) provides any clinical benefit in these settings is still being investigated. The evidence is limited to early phase trials. Larger trials are needed to establish the safety and efficacy of Opdivo (nivolumab) in these conditions.
- *Sarcoma (including osteosarcoma)*: The evidence for various soft tissue sarcomas (STS) including Ewing sarcoma, spindle cell sarcoma, and osteosarcoma, is limited to a single open-label, non-comparative phase 2 trial of Opdivo (nivolumab) with or without Yervoy (ipilimumab). The primary endpoint (ORR) was not met in the nivolumab monotherapy arm. [45] Additional trials are ongoing with combination therapy. [46,47]
- *Sequential therapy*: The study of Opdivo (nivolumab) in combination and in sequence with other immunotherapies and targeted therapies is underway. Early results appear promising; however, the optimal sequencing, patient selection, and overall benefit of combination therapies has not yet been determined.
    * There is an ongoing study of Opdivo (nivolumab) given sequentially with Yervoy (ipilimumab) in patients with advanced or metastatic melanoma [CHECKMATE-064 trial].
    * There is a phase 2 trial in progress that combines Sutent (sunitinib) plus Opdivo (nivolumab) in KIT-mutated advanced melanoma.
    * There is a study about to recruit that will compare the combination of Opdivo (nivolumab) with Tafinlar (dabrafenib) and/or Mekinist (trametinib).

REAUTHORIZATION CRITERIA:

- When coverage criteria are met, Opdivo (nivolumab) is authorized for six months (24 weeks) of therapy, after which time documentation must be provided to establish that the medication is effective. Specifically, there must be documentation of clinical benefit, including disease stability or improvement and there is a lack of disease progression, based on an assessment of change in tumor burden.
    * The standard of care for evaluation of response to cancer immunotherapy, such as Opdivo (nivolumab), is use of the iRECIST criteria for assessment of tumor burden. [6]
    * The iRECIST criteria include use of quantitative and qualitative criteria for assessment of change in tumor burden for target lesions and non-target lesions. [7]
        - Quantitative measurements for target lesions (tumor size and % change)
        - Qualitative evaluation for non-target lesions (present/disappeared/ unequivocal progression)
    * Documentation of benefit must include an assessment of the most recent imaging ("restaging scans") by the treating oncologist. Given the complexity of the evaluation, including use of the iRECIST criteria, Opdivo (nivolumab) will not be reauthorized without an assessment of response to therapy, such a partial response (iPR), complete response (iCR), or stable disease (iSD).
    * Use of immunotherapy may result in pseudoprogression, due to immune and T-cell activation, which can appear similar to tumor flare. If there is documentation of potential disease progression ["unconfirmed progressive disease (iUPD)"], a shortened authorization (up to three months) may be approved to allow time for

clarification of response to Opdivo (nivolumab), including clinical re-evaluation of the patient and reimaging. Guidelines recommend reimaging for iUPD after 4-8 weeks.

* If a patient has confirmed, unequivocal new lesions (progression of disease, iPD), additional Opdivo (nivolumab) is not coverable. If a new lesion is equivocal, iUPD reassessment by the treating oncologist with repeat imaging would apply (as noted above).

DOSING *[18]*

- As monotherapy, the dose of Opdivo (nivolumab) is 240 mg IV every 2 weeks in most all indications. Alternately, it may be given in a dose of 480 mg every 4 weeks or 360 mg every 3 weeks.
- When initially approved, Opdivo (nivolumab) dosing was based on weight; however, subsequent studies have shown that similar results are achieved with newly labeled flat dosing described above.
- The exception to flat dosing is when Opdivo (nivolumab) is administered in combination with Yervoy (ipilimumab). In this setting, lower weight-based doses (1 mg/kg or 3 mg/kg) are used and coverable doses mirror FDA-approved dosing (see *Quantity Limits* section).
- Therapy with Opdivo (nivolumab) is continued for three doses (cycles) when used as a neoadjuvant therapy for resectable NSCLC, up to one year when used in the adjuvant melanoma and esophageal cancer settings, up to two years when used in combination with Yervoy (ipilimumab) for MPM and NSCLC, and until disease progression or unacceptable toxicity when used in all other conditions (see *Quantity Limits* section).

Appendix 1: FDA- approved PD-1 and PD-L1 blocking monoclonal antibody therapies [a]
Programmed death receptor-1 (PD-1) inhibitors
Jemperli (dostarlimab)
Keytruda (pembrolizumab)
Libtayo (cemiplimab-rwlc)
Loqtorzi (toripalimab)
Opdivo (nivolumab)
Tevimbra (tislelizumab)
Zynyz (retifanlimab)
Programmed death-ligand 1 (PD-L1) inhibitor
Bavencio (avelumab)
Imfinzi (durvalumab)
Tecentriq (atezolizumab)

[a] Or as listed on the FDA.gov website

Cross References

Molecular Analysis for Targeted Therapy of Non-Small Cell Lung Cancer (NSCLC), Medical Policy Manual, Genetic Testing Policy No. 56
Adcetris, brentuximab vedotin, Medication Policy Manual, Policy No. dru264
Bavencio, avelumab, Medication Policy Manual, Policy No. dru499
Cabometyx, cabozantinib, Medication Policy Manual, Policy No. dru290
Imfinzi, durvalumab, Medication Policy Manual, Policy No. dru500
Jemperli, dostarlimab, Medication Policy Manual, Policy No. dru673
Keytruda, pembrolizumab, Medication Policy Manual, Policy No. dru367
Lenvima, lenvatinib, Medication Policy Manual, Policy No. dru398
Libtayo, cemiplimab-rwlc, Medication Policy Manual, Policy No. dru565
Opdualag, nivolumab-relatlimab, Medication Policy Manual, Policy No. dru718
Tecentriq, atezolizumab, Medication Policy Manual, Policy No. dru463
Yervoy, ipilimumab, Medication Policy Manual, Policy No. dru238
Zynyz, retifanlimab (Zynyz), Medication Policy Manual, Policy No. dru751

Codes	Number	Description
HCPCS	J9299	Nivolumab (Opdivo), 1 mg, injection

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Revision History

Revision Date	Revision Summary
9/19/2024	Effective 1/1/25: Changed reauthorization from 'may' to 'shall.' Operationally, all approvals will be for 24 weeks (six months). Ongoing therapy (beyond 24 weeks) will be subject to reauthorization review every 24 weeks, for documentation of disease stability or improvement and lack of disease progression.
9/19/2024	Effective 10/15/24: • Add coverage in front-line unresectable locally advanced or metastatic urothelial carcinoma when used in combination with cisplatin/ gemcitabine (new indication). • Add coverage criteria for "neoadjuvant/adjuvant therapy for resectable earlier stage NSCLC" [combined with the existing neoadjuvant criteria]. • Remove "adjuvant therapy for resectable earlier stage NSCLC" from the list of Investigational Uses.
6/20/2024	For clarity of coverage, added 'adjuvant therapy for resectable earlier stage NSCLC' to list of Investigational Uses. No change to intent of criteria.
3/21/2024	Added criteria for coverage of adjuvant Opdivo (nivolumab) for early-stage (IIB or IIC) melanoma, when used as a monotherapy, until disease progression, or for up to one year.
12/7/2023	• Added the requirement that RCC tumors have clear cell histology so coverage of Opdivo (nivolumab) aligns with coverage of Keytruda (pembrolizumab) in this setting, which does not change criteria intent. • Updated 'Neoadjuvant therapy for resectable cancer (NSCLC)' quantity limitation to read, 'In doses up to 360 mg every 3 weeks, for

Revision Date	Revision Summary
	up to three doses **in three months**'. The prior criterion stated, 'In doses up to 360 mg every 3 weeks, for up to three doses'. The updated language allows for dose delays during therapy. There is no change to the intent of the policy. • Added glioblastoma multiforme as investigational based on the results of a failed study.
12/9/2022	• Added coverage for Opdivo (nivolumab) in combination with platinum-based chemotherapy as a neoadjuvant therapy for resectable (tumors ≥ 4 cm or node positive) NSCLC (new indication). • Updated QL for new NSCLC use and for when used in combination with Yervoy (ipilimumab) to address tolerability issues evaluated in CheckMate 511.
9/23/2022	Added coverage criteria for Opdivo (nivolumab) as a combination therapy [with chemotherapy or ipilimumab (Yervoy)] for first-line treatment of ESCC, based on new evidence and a new FDA indication.
3/18/2022	Coverage criteria were added for adjuvant use of Opdivo (nivolumab) in muscle-invasive urothelial carcinoma (MIUC) with a high risk of recurrence (new indication).
10/15/2021	• Removed coverage of Opdivo (nivolumab) as a monotherapy for progressive, advanced hepatocellular carcinoma (HCC) based on the withdrawal of this indication from package labeling (clinical benefit not established in confirmatory trials). • Added coverage of Opdivo (nivolumab) for advanced gastric cancer, GEJ cancer, and esophageal adenocarcinoma for tumors with PD-L1 CPS ≥ 5 when used in combination with chemotherapy. • Added coverage of Opdivo (nivolumab) for up to one year for resectable (stage II or III) esophageal or GEJ cancer when used as adjuvant therapy (as a single agent) after neoadjuvant therapy with complete resection when there is residual pathologic disease. • Updated quantity limitations for new indications.

Revision Date	Revision Summary
4/21/2021	• Added coverage criteria for MPM and RCC (1st line, in combination with cabozantinib), new FDA indications (effective 5/15/2021). Because the new RCC indication expands use of nivolumab in RCC, existing coverage criteria for RCC were broadened to simplify administration of this policy. • The criteria under UC were simplified for more straight-forward application of the policy. Criteria were changed from defining coverage for specific treatment settings to a slightly broader, more general statement (disease progression on or following platinum-containing therapy). • The criteria under CRC were streamlined for easier application (the criterion pertaining to prior use of systemic therapy in the adjuvant setting was removed). • The criteria under HCC were streamlined for easier application (the criterion defining coverage based on separate Child-Pugh class ratings for nivolumab monotherapy and for combination nivolumab and ipilimumab therapy were combined). • The criteria under cHL were streamlined by removing the word 'autologous' as a descriptor for HSCT. This is a simplification and not a change to intent. • The criteria under melanoma were simplified by removing language specific to use in the adjuvant setting. There is no change to the intent of the policy (use in the adjuvant setting is still covered under the more general language). • Under the NSCLC criteria the requirement for documenting that 'no EGFR and ALK genomic tumor aberrations are present' was removed. This is a simplification and does not change the intent of the policy. • Removed coverage criteria for SCLC (FDA indication withdrawn) and added use in SCLC to list of 'Investigational uses. • Updated quantity limitations for new indications. • Updated COT language (no change to policy intent).
7/22/2020	• Added coverage criteria for use in advanced hepatocellular carcinoma (HCC). • Added coverage criteria for use in front-line metastatic NSCLC. • Added coverage criteria for use in esophageal squamous cell carcinoma (ESCC) as a monotherapy in the subsequent-line setting. • Updated quantity limitations for new indications. • Updated 'Investigational uses' (removed NSCLC, first-line)
6/15/2020	Removed references to brand Avastin from policy to account for upcoming changes in biosimilars policy (dru620).

Revision Date	Revision Summary
1/22/2020	• Added coverage for use in squamous cell anal carcinoma. • Clarified step therapy requirements for hepatocellular carcinoma. • Added continuation of therapy (COT) criteria.
10/23/2019	No changes to coverage criteria with this annual update.
10/19/2018	• Added coverage for use in metastatic SCLC (new indication). • Updated quantity limitations for new indication. • Updated 'Investigational uses' (removed SCLC).
8/17/2018	• Added coverage criteria for use in MSI-H metastatic CRC and advanced RCC when used in combination with Yervoy (ipilimumab). • Updated "Investigational uses" (removed front-line use in RCC). • Updated the 'Administration, Quantity Limitations, and Authorization Period' section to include the new front-line RCC and CRC (in combination with Yervoy) indications.
4/20/2018	• Added coverage criteria for subsequent treatment of hepatocellular carcinoma, and adjuvant therapy for resectable melanoma. • Dosing and quantity limitations were updated to reflect use in the two additional settings listed above. • Clarified authorization is valid "until disease progression" (no change to intent). • The list of investigational uses was updated to include SCLC and front-line use in RCC.
3/16/2018	Update dosing (240 mg every 2 weeks or 480 mg every 4 weeks).
11/10/2017	• Coverage criteria were updated to include MSI-H/dMMR metastatic CRC. • The investigational uses and Quantity Limitation sections of the policy were also updated as they relate to MSI-H/dMMR CRC.
9/8/2017	• Coverage criteria updated for Hodgkin lymphoma (HL) to reflect currently available evidence and to make consistent with HL criteria in the pembrolizumab medication policy. • NSCLC coverage criteria regarding prerequisite therapies was clarified to reflect the standard of care and currently available evidence. In patients with EGFR or ALK mutations, front-line treatment with appropriate EGFR or ALK TKI therapy, followed by platinum-based chemotherapy, is the standard of care. This is consistent with the sequencing used in the study population.
3/10/2017	• Added criteria for coverage in HNSCC and bladder cancer. • Updated NSCLC criteria such that prior use of a PD-L1 inhibitor precludes coverage.
10/13/16	Updated QL to be in line with FDA labeling change that occurred on 9/15/16.

Revision Date	Revision Summary
9/9/2016	Add policy coverage criteria for classical Hodgkin lymphoma (CHL), a new FDA indication, and remove it as an 'investigational' use.
3/11/2016	• The coverage criteria for Opdivo in melanoma were reorganized; however, the intent of the criteria was not altered. • Several appendices were combined and then updated to include renal cell carcinoma (RCC) therapies. • The appendix describing the different NSCLC histologies was deleted.
12/11/2015	• Add policy coverage for new FDA indications: - Use in combination with Yervoy for melanoma - Use in nonsquamous NSCLC - Use in RCC • Add criteria to prevent the use of sequential therapy of PD1s (Opdivo/Keytruda). • Add Appendix 1, with a list of available PD1s. • Add Appendix 3, with a list of other targeted therapies for melanoma (modified the table of BRAF inhibitors).

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Medication Policy Manual | **Policy No:** dru393

Topic: Xgeva, denosumab | **Date of Origin:** March 13, 2015

Committee Approval Date: September 19, 2024 | **Next Review Date:** 2025

Effective Date: December 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Xgeva (denosumab) is a medication used to prevent skeletal complications of bone metastases from solid tumor cancers and multiple myeloma. In addition, it is also used for the treatment of giant cell tumor of the bone and hypercalcemia of malignancy. It is a monoclonal antibody that targets the receptor activator of nuclear factor kappa B ligand (RANKL). Xgeva (denosumab) prevents RANKL from activating its receptor, RANK, on the surface of osteoclasts, their precursors, and osteoclast-like giant cells.

PLEASE NOTE: Denosumab is also marketed as Prolia and is used treat osteoporosis (bone loss). There is a separate medication policy for Prolia (denosumab) for these indications, specifically. See policy dru223.

Policy/Criteria

Most contracts require pre-authorization approval of Xgeva (denosumab) prior to coverage.

I. Continuation of therapy (COT): Xgeva (denosumab) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New Starts (treatment-naïve patients): Xgeva (denosumab) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criterion A, B, or C is met.

A. Prevention of **skeletal related events** (SRE; such as fractures) in patients with:

1. Bone metastases from any solid tumor or multiple myeloma.

AND

2. Prior treatment with an IV bisphosphonate [e.g., pamidronate or Zometa (zoledronic acid)] has been ineffective, contraindicated, or not tolerated.

PLEASE NOTE: Ineffective is defined as having a skeletal related event while on bisphosphonate therapy. Cancer progression is NOT considered a lack of efficacy. A contraindication to IV bisphosphonates may include, but is not limited to, creatinine clearance of less than 35 ml/min.

OR

B. Treatment of **giant cell tumor of the bone** when:

1. The tumor is unresectable.

OR

2. The tumor is resectable, but surgical resection is documented as medically contraindicated.

OR

C. Treatment of **hypercalcemia of malignancy** when:

1. The albumin-corrected calcium is above 12.5 mg/dL (3.1 mmol/L) (see *Appendix 1).*

AND

2. Prior treatment with an IV bisphosphonate [e.g., pamidronate or Zometa (zoledronic acid)] has been ineffective, contraindicated, or not tolerated.

PLEASE NOTE: Ineffective is defined as having persistent hypercalcemia despite bisphosphonate therapy. Cancer progression is NOT considered a lack of efficacy. A contraindication to IV bisphosphonates may include, but is not limited to, creatinine clearance of less than 35 ml/min.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Xgeva (denosumab) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved Xgeva (denosumab) may be authorized:

1. In quantities up to 13 of the 120 mg injections per year for the prevention of complications of bone metastases (SREs) from solid tumor cancers or multiple myeloma.

2. In quantities up to 15 of the 120 mg injections per year for the treatment of giant cell tumor of the bone and hypercalcemia of malignancy.

C. Authorization **may** be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

IV. Xgeva (denosumab) is considered not medically necessary for the treatment of osteoporosis.

V. Xgeva (denosumab) is considered investigational when used for all other conditions.

Position Statement

Summary

- Xgeva (denosumab) is a monoclonal antibody used for the prevention of skeletal related events (SREs) in patients with bone metastases from solid tumor cancers (e.g., breast cancer, prostate cancer) or multiple myeloma. It is also used for the treatment of giant cell tumor of the bone and hypercalcemia of malignancy.
- Generic IV bisphosphonates (pamidronate and zoledronic acid) provide the best value for prevention of skeletal related events (SREs; such as fractures) in patients with solid tumors or multiple myeloma.
- There is insufficient evidence of superior safety or tolerability of Xgeva (denosumab) over bisphosphonates. Both have a risk of osteonecrosis of the jaw (ONJ).
- There is reliable evidence that Xgeva (denosumab) is a potent antiresorptive therapy for the prevention of SREs in patients with some cancers. The effect is consistent across the placebo-controlled trials and comparative, non-inferiority trials. However, there uncertainty in the evidence with regard to whether Xgeva (denosumab) is better than other available treatment options.
- Xgeva (denosumab) and zoledronic acid (generic Zometa) appear to be at least similar in delaying the time to first skeletal related event (SRE) in patients with metastases from solid tumor cancers; however, the clinical relevance of delaying the time to first SRE is uncertain relative to prevention of SREs, reduction in the number of SREs, or overall survival.
- The evidence for efficacy for Xgeva (denosumab) for the treatment of giant cell tumor of the bone comes from two open-label trials that demonstrated a decrease in tumor size in 25% of patients. Patients in the trials had e giant cell tumor of the bone that was either recurrent, unresectable, or for which planned surgery was likely to result in severe morbidity.
- The evidence for efficacy for Xgeva (denosumab) for hypercalcemia of malignancy comes from a single-arm trial in patients refractory to treatment with prior IV bisphosphonate therapy. Xgeva (denosumab) was associated with lowering corrected serum calcium 63.6% of patients treated with at day ten.
- The recommended dose of Xgeva (denosumab) for prevention of skeletal-related events in multiple myeloma and bone metastasis from solid tumors is 120 mg every four weeks. For giant cell tumor of the bone and hypercalcemia of malignancy, the recommended dose is 120 mg every four weeks with additional 120 mg doses on days 8 and 15 of the first month of therapy.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit

relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.

- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy

CANCER-RELATED BONE METASTASES

Metastatic Breast and Prostate Cancer:

- The effectiveness of Xgeva (denosumab) for bone metastases from breast or prostate cancer relative to zoledronic acid was evaluated in two low confidence, randomized, double-blind, non-inferiority trials that included 2,046 women with bone metastases from breast cancer and 1,904 men with metastatic prostate cancer. [1,2]
    * The primary endpoint in both trials was the non-inferiority of Xgeva (denosumab) relative to zoledronic acid for time to first SRE (defined as bone pain, pathologic fractures, spinal cord compression, and bone complications that required radiation or surgery).

Breast Cancer:

- Xgeva (denosumab) was shown to be at least similar to zoledronic acid for delaying the time to first SRE in patients with metastatic breast cancer and metastatic prostate cancer. The study authors concluded that Xgeva (denosumab) was superior to zoledronic acid for delaying time to first SRE; however, the evidence is of insufficient quality to validate that conclusion. There was no difference between treatment groups for overall survival or disease progression. [2]
- The National Comprehensive Cancer Network (NCCN) Breast Cancer guideline recommends that Xgeva (denosumab), zoledronic acid, or pamidronate (all with calcium and vitamin D supplementation) should be given in addition to chemotherapy or endocrine therapy if bone metastasis is present. There is no preference given to one agent over the other, as all are considered a category 1 recommendation. [3]
- The American Society of Clinical Oncology (ASCO) guideline recognizes Xgeva (denosumab), pamidronate and zoledronic acid as treatment options for patients with breast cancer with evidence of bone metastases. Per the ASCO guideline, there is insufficient evidence to demonstrate greater efficacy of one product over another for the prevention and treatment of skeletal-related events. [4]

Prostate Cancer:

- There is low confidence in the evidence that Xgeva (denosumab) is superior to zoledronic acid because the clinical relevance of delaying the time to first SRE is uncertain, particularly in the absence of improved overall survival or disease progression. Additional concerns with the studies include high attrition and the potential for suboptimal dosing of zoledronic acid. [1]
- The NCCN Prostate Cancer guideline recommends both zoledronic acid (category 2A recommendation) and Xgeva (denosumab) (category 1 recommendation) for the prevention of skeletal-related events in patients with prostate cancer if bone metastases is present. [5] However, there is low confidence in the evidence that Xgeva (denosumab) is superior to zoledronic acid.

Other Solid Tumor Cancers and Multiple Myeloma:

- The effectiveness of Xgeva (denosumab) relative to zoledronic acid was evaluated in a low confidence, randomized, double-blind, non-inferiority trial that included 1,779 patients with bone metastases from various advanced solid tumor cancers (excluding breast or prostate cancer) or patients with multiple myeloma. [6]
    * The primary endpoint was the non-inferiority of Xgeva (denosumab) relative to zoledronic acid for time to first SRE.
    * Xgeva (denosumab) was shown to be non-inferior to zoledronic acid for time to first SRE. There was no difference between treatment groups for overall survival or disease progression.
    * The trial is considered low confidence because the clinical relevance of delaying the time to first SRE is uncertain, particularly in the absence of improved overall survival or disease progression. Additional concerns with the study include high attrition and the potential for suboptimal dosing of zoledronic acid.
    * In a subgroup analysis of patients with multiple myeloma (n = 180), an increase in mortality was observed with Xgeva (denosumab) relative to zoledronic acid. [7] A follow-up non-inferiority trial demonstrated the non-inferiority of Xgeva (denosumab) compared to zoledronic acid. No difference in mortality was observed. [7]

GIANT CELL TUMOR OF THE BONE:

- The safety and efficacy of Xgeva (denosumab) was evaluated in 282 adult or skeletally mature adolescent patients with giant cell tumor of the bone.
    * Two open-label, uncontrolled trials studied Xgeva (denosumab) in patients with giant cell tumor of the bone that was recurrent, unresectable, or for which surgery would likely result in morbidity. [8,9]
    * Objective response rate (decrease in tumor size) was evaluated as the primary efficacy endpoint. The overall objective response rate was 25%, and all responses were partial responses. [7-9]
- The NCCN Bone Cancer guideline recognizes Xgeva (denosumab) as a category 2A recommendation for giant cell bone tumors that are unresectable or are resectable with unacceptable morbidity. Interferon, peg-interferon, radiation therapy, and observation are also listed as category 2A recommendations in these treatment settings. [10]

HYPERCALCEMIA OF MALIGNANCY:

- The safety and efficacy of Xgeva (denosumab) was demonstrated in an open-label, single-arm trial in 33 patients with hypercalcemia of malignancy (with or without bone metastases). [7,11]
    - ***** Patients were refractory to treatment with IV bisphosphonate therapy. Refractory hypercalcemia of malignancy was defined as albumin-corrected calcium of > 12.5 mg/dL (3.1 mmol/L) despite treatment with IV bisphosphonate in the seven to thirty days prior to initiation of Xgeva (denosumab) therapy.
    - ***** The primary outcome measure was the proportion of patients achieving a response, defined as corrected serum calcium ≤ 11.5 mg/dL (2.9 mmol/L), within ten days after Xgeva (denosumab) administration.
    - ***** A total of 21 out of 33 patients (64%) had a response to Xgeva (denosumab) treatment within ten days.

Investigational Uses

- Denosumab is also marketed as Prolia and is indicated for the treatment of osteoporosis. Use of Xgeva for this indication is considered not medically necessary as dosage and frequency of administration differ between indications and products.
- The use of Xgeva (denosumab) for all other conditions is considered investigational.

Safety [7]

- Both bisphosphonates and Xgeva (denosumab) have labeled warnings for risk of osteonecrosis of the jaw (ONJ).
    - ***** As noted in the NCCN prostate cancer and breast cancer guidelines, ONJ is seen with both Xgeva (denosumab) and bisphosphonates.
    - ***** Poor baseline dental health or dental procedures during treatment are known risk factors for ONJ. Thus, patients should be referred for dental evaluation before starting either agent.
    - ***** A position paper from the American Association or Oral and Maxillofacial Surgeons (AAOMS) states that the risk for ONJ among cancer patients exposed to Xgeva (denosumab) is comparable to the risk of ONJ in patients exposed to zoledronic acid. [12]
- Xgeva (denosumab) can cause severe symptomatic hypocalcemia, and fatal events have occurred. All patients should be adequately supplemented with calcium and vitamin D when appropriate.

Appendix 1: Equation for determining the albumin-corrected calcium

Calcium Correction Equation
Corrected Calcium = Serum Ca + 0.8 * (Normal Albumin – Patient Albumin) [a,b] Corrected Calcium Calculators: http://www.globalrph.com/calcium.htm http://www.uptodate.com/contents/calculator-calcium-correction-in-hypoalbuminemia (with subscription)

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Xgeva, denosumab, BlueCross BlueShield Association Specialty Pharmacy Combined Capacity (SPCC) Report # 15-2010. December 2010.
Prolia, denosumab, Medication Policy Manual, Policy No. dru223
Anabolic Bone Medications, Medication Policy Manual, Policy No, dru612

Codes	Number	Description
HCPCS	J0897	Injection, denosumab (Xgeva), 1 mg

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Revision History

Revision Date	Revision Summary
09/19/2024	No criteria changes with this annual review.
9/14/2023	No criteria changes with this annual review.
9/23/2022	No criteria changes with this annual update.
10/15/2021	Updated COT. No criteria changes with this annual update.
10/28/2020	Added COT criteria. No change to intent of policy.
10/23/2019	Clarification of policy language (no changes to criteria intent with this annual update)
1/18/2018	Coverage criteria for prevention of skeletal-related events in multiple myeloma added.
3/10/2017	No criteria changes with this annual update.
3/11/2016	No criteria changes with this annual update.

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Medication Policy Manual | **Policy No:** dru408

Topic: Site of Care Review | **Date of Origin:** July 10, 2015

Committee Approval Date: September 19, 2024 | **Next Review Date:** 2025

Effective Date: January 1, 2025

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

Description

This policy is to review the requested site of care (SOC) for provider-administered medications. Many medications historically infused in hospital-based infusion centers have been evaluated and determined to be safe for infusion outside of hospital-based settings. Use of non-hospital-based infusion centers and home infusion services is an accepted standard medical practice and sometimes referred to as an "alternate site of care." These settings offer high-quality services for patients and reduce the overall cost of care, as compared to costly hospital-based infusion centers.

This policy applies to fully-insured commercial and exchange plans, and the Washington State Health Care Authority (with the exception of Uniform Medical Plan Plus), based in Washington, Oregon, Idaho, and Utah. This policy may apply to other self-insured groups [a.k.a. administrative services only (ASO), depending on the group-specific benefit]. This policy does **not** apply to Medicare plans.

Policy/Criteria

I. Under most contracts, medications included in the infusion drug site of care program (see *Appendix 1*) may be considered medically necessary when individual medication policy criteria are met (if applicable) **AND** one of the following criterion A or B below are met**:**

A. The medication is administered in an approved site of care. (No formal "Site of Care" review is required)

OR

B. The medication is administered in an unapproved site of care (see *Appendix 2*), such as an unapproved hospital-based infusion center, when at least one of the criterion below (1, 2, or 3) are met:

NOTE: Site of care review criteria will be waived for payment of the initial dose(s) of a medication given during the first 30 days (starting from the date of the first dose) after the medication has been approved for pre-authorization, to allow for adequate transition time to an approved site of care for subsequent doses.

1. An approved site of care is not accessible to the member, as documented by criteria a **AND** b, being met:

a. The provider is not aware of an approved site of care that can administer the drug. Approved sites of care include, but are not limited to provider's offices or ambulatory infusion sites.

AND

b. The member's home is not eligible for home infusion services for reasons including, but not limited to: the home is not within the service area of the home infusion provider or is deemed unsuitable for care by the home infusion provider, unless the medication is not eligible for home infusion services (see *Appendix 1*).

OR

2. Clinical documentation of at least one **long-term medical reason** (specifically, medical conditions that will not change) why an approved site of care is not an option, including, but not limited to:

a. Significant behavioral issues and/or cognitive impairment including, but not limited to, those associated with developmental delay, down syndrome, dementia, or excessive anxiety such as severe needle phobia.

b. Prior severe infusion reactions, despite standard pre-medications.

c. Presence of circulating antibodies which may increase risk of infusion reactions.

d. Documented difficult IV access.

e. Treatment of Kawasaki disease.

OR

3. Clinical documentation of <u>at least one</u> **short-term medical reason** (specifically, medical conditions/rationale that will change with time) why an approved site of care is not an option, including, but not limited to:

- **a.** The member less than 14 years of age.
- **b.** Treatment within 100 days after hematopoietic stem cell transplantation (HSCT, a.k.a. bone marrow transplant).
- **c.** Concurrent treatment with medications that require a higher level of monitoring (such as CAR T-cell therapy, intravenous cytotoxic chemotherapy, or blood products).
- **d.** Treatment of antibody-mediated rejection (a.k.a. vascular rejection, acute humoral rejection) following a solid organ transplant.
- **e.** Acute treatment of vision changes (or high-risk of, based on disease stated).

II. Limitations and Authorization Period.

A. For exceptions approved under criterion I.B.1. above **(no known approved sites of care and no home infusion option)**, authorization **<u>shall</u>** be reviewed at least annually to confirm that current medical necessity criteria are met, including that an approved site of care is still not a treatment option.

B. For exceptions approved under criteria I.B.2. above **(long-term medical reason)**, authorization **<u>may</u>** be reviewed at least annually to confirm that current medical necessity criteria are met, including that an approved site of care is still not a treatment option.

C. For exceptions approved under criteria I.B.3. above **(short-term medical reason)**, authorization will be as follows:

Medical reason	Authorization Period	Reauthorization of the SOC exception
Member is less than 14 years of age	Until date member turns 14 years of age	None. Any request after the 14th birthday will be subject to a new, full Site of Care Exception review.
Treatment within 100 days after HSCT	100 days, based on the date of HSCT	None. Any extension will be subject to a new, full Site of Care Exception review, based on the criteria listed in I.B.2.
Concurrent treatment with medications that require a higher level of monitoring	6 months	Authorization **<u>shall</u>** be reviewed at least every 6 months to confirm that current medical necessity criteria are met, including that an approved site of care is still not a treatment option.
Treatment of antibody-mediated rejection	6 months	None. Any additional treatment course will be subject to a new, full Site of Care Exception review.
Acute treatment of vision changes	3 months	None. Any additional treatment course will be subject to a new, full Site of Care Exception review.
Other short-term medical reason	3 months	Authorization **<u>shall</u>** be reviewed at least every 3 months to confirm that current medical necessity criteria are met, including that an approved site of care is still not a treatment option.

III. The medications in the infusion drug site of care program are considered not medically necessary if administered in an unapproved site of care, such as an unapproved hospital-based infusion center, when an approved site of care (e.g., physical sites or home infusion) is a treatment option.

Position Statement

- New pharmaceuticals requiring infusion therapy, may be administered safely, effectively, and much less costly outside of hospital-based infusion centers (a.k.a. hospital outpatient settings). Sites of care such as doctor's offices, infusion centers, home infusion, and approved hospital-based infusion centers are well-established, accepted by physicians, and provide the best value to patients to reduce the overall cost of care.
- A site of care exception for an infusion at an unapproved site of care location must be requested by the provider and reviewed by the health plan prior to administration of the infused medication, per the terms of the member contract with the health plan.

Site of Care Review:

- Use of non-hospital-based infusion centers and home infusion services is an accepted standard medical practice. These sites offer high-quality services for patients and reduce the overall cost of care, as compared to costly hospital-based infusion centers. [1-8]
- All medications infused outside of a hospital setting have undergone an evaluation for safe infusion and development of infusion standards, including adverse drug reaction management and reporting algorithms.
- At all sites of care, every patient undergoes an assessment during the intake process by the infusion provider, which includes evaluation of individual clinical assessment parameters. These parameters may include, but are not limited to, previous tolerance of products (such as IVIG), assessment of kidney function, risk factors for developing thromboembolic events, and venous access. [9-10]
- For use of home infusion services, an assessment is conducted to determine if the home is a safe, appropriate site of care, with adequate support for infusion in the home.
- Because providers need time to arrange for assessment and coordination of care, the first dose of provider-administered medications may be covered in a hospital-based infusion center, if needed, to allow adequate time for a seamless transition of care. This may include arranging for delivery of medications, appointment scheduling, and/or patient education, such as for self-administration of medications such as subcutaneous immune globulin (SCIG).
- Claims submitted for infusion services performed at an unapproved site of care, such as an unapproved hospital-based infusion center (such as on-campus or off-campus hospital outpatient settings, denoted by place of service codes 22 or 19; see *Appendix 3*), are considered not medically necessary when an approved site of care is a treatment option or when preauthorization for the unapproved site of care had not been requested for review. This is waived for claims given during the first 30 days (starting from the date of the first dose) after the medication has been approved for pre-authorization, to allow for adequate transition time to an approved site of care for subsequent doses.

- Pediatric patients often differ from adult patients in physiology, development, and cognitive and emotional function. They may also require doses, infusion rates, and equipment that vary and differ compared to adult patients. Special infusion training and expertise is needed. Therefore, this policy allows for patients under 14 years to obtain infusion services in approved sites of care or unapproved sites of care, such as unapproved hospital-based infusion centers.
- Clinical criteria considered for site of care exception review, aside from young age, include long-term and short-term medical reasons. Long-term medical reasons are not expected to change with time, such as behavioral issues or infusion reactions to the specific drug. Short-term medical reasons for a site of care exception would change over time; therefore, short-term medical reason requests would be re-reviewed as outlined by the authorization periods defined above in Section II.C.

Appendix 1: Medications Included in the Infusion Drug Site of Care Program

Medication	Effective Date	Policy Number	Home infusion eligible [b]	HCPCS Code
Actemra, tocilizumab [a]	3/1/2015	dru444, dru900 (UMP)	Yes	J3262
Adakveo, crizanlizumab-tmca	5/15/2020	dru628	Yes	J0791
Aldurazyme, laronidase	4/1/2016	dru426	Yes	J1931
Amondys 45, casimersen	10/1/2024	dru661	Yes	J1426
Amvuttra, vutrisiran	10/1/2024	dru733	Yes	J0225
Aralast NP, alpha-1 proteinase inhibitor	10/1/2024	dru382	Yes	J0256
Asceniv, immune globulin	10/1/2019	dru020	Yes	J1554
Avsola, infliximab-axxq	1/1/2021	dru620	Yes	Q5121
Benlysta IV, belimumab	10/1/2024	dru789	Yes	J0490
Bivigam, immune globulin	3/1/2015	dru020	Yes	J1556
Briumvi-xiiy, ublituximab-xiiy	4/15/2023	dru753, dru907 (UMP)	Yes	J2329
Carimune NF, immune globulin	3/1/2015	dru020	Yes	J1566
Cerezyme, imiglucerase	4/1/2017	dru649	Yes	J1786
Cimzia, certolizumab pegol [a]	1/1/2017	dru444, dru900 (UMP)	Yes	J0717
Cinqair, reslizumab	1/1/2022	dru538	Yes	J2786
Cinryze**,** plasma-derived C1-INH	10/1/2024	dru535	Yes	J0598
Cosentyx, secukinumab	1/1/2025	dru444, dru900 (UMP)	Yes	J3247
Cutaquig, immune globulin	10/1/2019	dru020	Yes	J1551
Cuvitru, immune globulin	9/15/2016	dru020	Yes	J1555
Elaprase, idursulfase	4/1/2016	dru426	Yes	J1743
Elelyso, taliglucerase alfa	10/1/2024	dru649	Yes	J3060
Elfabrio, pegunigalsidase alfa-iwxj	1/1/2024	dru575	Yes	J2508
Enjaymo, sutimlimab	10/1/2024	dru716	Yes	J1302
Entyvio, vedolizumab	7/10/2015	dru444, dru900 (UMP)	Yes	J3380

Medication	Effective Date	Policy Number	Home infusion eligible [b]	HCPCS Code
Evenity, romosozumab-aqqg	10/1/2019	dru612	Yes	J3111
Exondys 51, eteplirsen	10/1/2024	dru480	Yes	J1428
Fabrazyme, agalsidase beta	7/1/2015	dru575	Yes	J0180
Fasenra, benralizumab [a]	1/1/2022	dru538	Yes	J0517
Flebogamma, immune globulin	3/1/2015	dru020	Yes	J1572
Gammagard, immune globulin	3/1/2015	dru020	Yes	J1569
Gammagard S/D, immune globulin	3/1/2015	dru020	Yes	J1566
Gammaked, immune globulin	3/1/2015	dru020	Yes	J1561
Gammaplex, immune globulin	3/1/2015	dru020	Yes	J1557
Gamunex/Gamunex-C, immune globulin	3/1/2015	dru020	Yes	J1561
Givlaari, givosiran	10/1/2024	dru630	Yes	J0223
Glassia, alpha-1 proteinase inhibitor	10/1/2024	dru382	Yes	J0257
Hizentra, immune globulin	3/1/2015	dru020	Yes	J1559
Hyqvia, immune globulin	3/1/2015	dru020	Yes	J1575
Ilaris, canakinumab	10/1/2024	dru677	Yes	J0638
Ilumya, tildrakizumab-asmn	10/1/2024	dru444, dru900 (UMP)	Yes	J3245
Immune globulin (IVIG, SCIG)	3/1/2015	dru020	Yes	J1459, J1555, J1556, J1557, J1559, J1561, J1566, J1568, J1569, J1572, J1575, J1599
Inflectra, infliximab-dyyb	1/1/2017	dru620	Yes	Q5103
Ixifi, infliximab-qbtx	10/1/2018	dru620	Yes	Q5109
Kanuma, sebelipase alfa	6/10/2016	dru426	Yes	J2840
Leqvio, inclisiran	6/1/2022	dru697	Yes	J1306
Lumizyme, alglucosidase alfa	7/1/2015	dru426	Yes	J0221
Nexviazyme, avalglucosidase alfa-ngpt	1/1/22	dru426	Yes	J0219
Nucala, mepolizumab [a]	1/1/2022	dru538	Yes	J2182
Ocrevus, ocrelizumab	9/1/2018	dru753, dru902 (UMP)	Yes	J2350
Octagam, immune globulin	3/1/2015	dru020	Yes	J1568
Onpattro, patisiran	10/1/2024	dru733	Yes	J0222
Orencia, abatacept [a]	3/1/2015	dru444, dru900 (UMP)	Yes	J0129
Panzyga, immune globulin	9/1/2018	dru020	Yes	J1599, J1576
Pombiliti, cipaglucosidase alfa	4/15/2024	dru426	Yes	J1203
Privigen, immune globulin	3/1/2015	dru020	Yes	J1459
Prolastin-C, alpha-1 proteinase inhibitor	10/1/2024	dru382	Yes	J0256
Radicava IV, edaravone [a]	8/11/2017	dru510	Yes	J1301
Reblozyl, luspatercept	5/15/2020	dru631	Yes	J0896
Remicade, infliximab	3/1/2015	dru620	Yes	J1745
Renflexis, infliximab-abda	8/11/2017	dru620	Yes	Q5104
Rystiggo (rozanolixizumab),	1/15/2024	dru696	Yes	J1412

Medication	Effective Date	Policy Number	Home infusion eligible [b]	HCPCS Code
Saphnelo, anifrolumab-fnia	1/1/2022	dru688	Yes	J0491
Simponi Aria, golimumab [a]	3/1/2015	dru444, dru900 (UMP)	Yes	J1602
Soliris, eculizumab	5/1/2015	dru385	Yes	J1300
Tepezza, teprotumumab-trbw	5/15/2020	dru632	Yes	J3241
Tezspire, tezepelumab-ekko	10/1/2024	dru538	Yes	J2356
Tofidence, tocilizumab-bavi	1/1/2025	dru444, dru900 (UMP)	Yes	Q5133
Tyenne, tocilizumab-aazg	1/1/2025	dru444, dru900 (UMP)	Yes	J3590
Ultomiris, ravulizumab-cwvz	7/1/2019	dru385	Yes	J1303
Uplizna, inebilizumab- cdon	1/1/2021	dru657	Yes	J1823
Trogarzo, ibalizumab-uiyk	10/1/2024	dru789	Yes	J1746
Viltepso, viltolarsen	10/1/2024	dru640	Yes	J1427
VPRIV, velaglucerase alfa	4/1/2017	dru649	Yes	J3385
Vyepti, eptinezumab	1/1/2022	dru540	Yes	J3032
Vyondys 53, golodirsen	10/1/2024	dru606	Yes	J1429
Vyvgart, efgartigimod	7/15/2022	dru696	Yes	J9332
Vyvgart Hytrulo, efgartigimod alfa and hyaluronidase-qvfc	1/1/2024	dru696	Yes	J9334
Vyjuvek, beremagene geperpavec-svdt	1/1/2024	dru759	Yes	J3401
Xembify, immune globulin	5/15/2020	dru020	Yes	J1558
Xolair, omalizumab [a]	1/1/2022	dru538	Yes	J2357
Zemaira, alpha-1 proteinase inhibitor	10/1/2024	dru382	Yes	J0256

[a] This policy only applies to the formulations of these medications covered under the medical benefit. Formulations for self-administration may be available through the pharmacy benefit for most members.
[b] As of the date of the policy publication.

Appendix 2: Glossary

Term	Description
Approved site of care	Location where medications are safely and effectively administered by a health care professional. Approved sites of care include: • Doctor's offices • Standalone ambulatory infusion centers • Home infusion • Approved hospital-based infusion centers
Unapproved site of care	Location where medications are administered by a professional and the facility is reimbursed for the medication and services at a much higher rate than approved sites of care. Unapproved sites of care include: • Unapproved hospital-based infusion centers (denoted by place of service codes 22 or 19; see *Appendix 3*)

Appendix 3: Place of Service Codes and Descriptions [11]

Place of Service Code	Place of Service Name	Description
11	Office	Location, other than a hospital, skilled nursing facility (SNF), military treatment facility, community health center, State or local public health clinic, or intermediate care facility (ICF), where the health professional routinely provides health examinations, diagnosis, and treatment of illness or injury on an ambulatory basis.
12	Home	Location, other than a hospital or other facility, where the patient receives care in a private residence.
19	Off Campus-Outpatient Hospital	A portion of an off-campus hospital provider-based department which provides diagnostic, therapeutic (both surgical and nonsurgical), and rehabilitation services to sick or injured persons who do not require hospitalization or institutionalization.
22	On Campus-Outpatient Hospital	A portion of a hospital's main campus which provides diagnostic, therapeutic (both surgical and nonsurgical), and rehabilitation services to sick or injured persons who do not require hospitalization or institutionalization.

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Revision History

Revision Date	Revision Summary
9/19/2024	• Added Cosentyx, Tofidence, and Tyenne to policy (effective 1/1/25). • Updated Pombiliti HCPCS code in Appendix 1.
6/20/2024	Added Tezspire, Cinryze, Amvuttra, Ilaris, Ilumya, Amondys 45, Exondys 51, Viltepso, Vyondys, Elelyso, Givlaari, Onpattro, Enjaymo, Glassia, Prolastin-C, Aralast NP, Zemaira, Benlysta IV, and Trogarzo to policy (effective 10/1/2024).
3/21/2024	Added Pombiliti (cipaglucosidase alfa) to policy.
12/7/2023	Added Rystiggo (rozanolixizumab) to policy.
9/14/2023	Added Elfabrio (pegunigalsidase alfa-iwxj), Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc), and Vyjuvek (beremagene geperpavec-svdt) to policy.
6/15/2023	Updated policy numbers in Appendix 1 for Briumvi (ublituximab-xiiy) and Ocrevus (ocrelizumab) for new combination policy dru753 (effective 9/1/2023).
3/16/2023	Added Briumvi-xiiy, ublituximab-xiiy to policy effective 4/15/2023.
12/9/2022	• Modified status of administrative services only (ASO) groups. • Updated HCPCS codes in Appendix 1. • Removed the following medications from the policy (effective 1/15/2023): Crysvita (burosumab-twza), Elelyso (taliglucerase alfa), Naglazyme (galsulfase), Onpattro (patisiran), Revcovi (elapegademase-lvlr), and Vimizim (elosulfase alfa).
6/17/2022	• Added Vyvgart (efgartigimod) to policy effective 7/15/2022. • Updated HCPCS and policy numbers in Appendix 1.
3/18/2022	Added Leqvio (inclisiran) to policy (effective 6/1/2022).
10/15/2021	• Added Xolair, Vyepti, Cinqair, Nucala, Fasenra, and Saphnelo to policy effective 1/1/2022. • Clarified policy criteria. No changes to intent of criteria. • Updated dru policy numbers as needed. • Updated HCPCS code for Adakveo. • Added UMP policy numbers.
7/16/2021	Effective 8/15/2021: • Updated the lines of business impacted by this program. • Updated access requirements for administration at non-approved sites of care (Criteria B.1.). • Removed Adagen (pegademase bovine), Myozyme (alglucosidase alfa), Prolia (denosumab), and Tysabri (natalizumab) from program.
10/28/2020	• Added Avsola (infliximab-axxq) and Uplizna (inebilizumab) to policy (effective 1/1/2021). • Clarified policy criteria. No changes to intent of criteria. • Updated dru policy numbers as needed.

Revision Date	Revision Summary
7/22/2020	• Removed Trogarzo (ibalizumab-uiyk) from policy (effective 8/15/20). Trogarzo policy to be archived effective 8/15/2020.
6/1/2020	• Updated Appendix 1 with correct effective dates and HCPCS codes.
4/22/2020	• Added Adakveo (crizanlizumab), Reblozyl (luspatercept), and Tepezza (teprotumumab-trbw) to the policy.
1/22/2020	• Clarified situations where no SOC review is needed. • Added medical exception criteria for acute treatment of vision-threatening disease. • Updated exception authorization periods.
7/24/2019	Added Crysvita (burosumab) and Evenity (romosozumab) to the policy.
4/25/2019	Added Revcovi (elapegademase) and Ultomiris (ravulizumab) to the policy.
1/31/2019	• Added Onpattro (patisiran) to the policy, effective 4/1/2019. • Updated Appendix 1 HCPCS codes.
8/17/2018	No criteria changes on this annual review.
6/15/2018	• Clarified home infusion criteria I.B.1.b only applies to medications eligible for home infusion. • Updated Appendix 1 to include home infusion eligibility.
5/18/2018	• No change to intent of coverage criteria. Clarification of description, policy language, and addition of applicable J-codes. Defined approved and unapproved sites of care. • Added the following medications to the policy: o Effective 6/1/2018: Trogarzo (ibalizumab-uiyk). o Effective 9/1/2018: Elelyso (taliglucerase alfa), Ocrevus (ocrelizumab). o Effective 10/1/2018: Ixifi (infliximab-qbtx). • Clarified medical exception criteria for concurrent cancer immunotherapy, including CAR T-cell therapy, and age less than 13 years old.
8/11/2017	Updated Appendix 1.
1/17/2017	Removed Lemtrada and Exondys from site of care program.
12/16/2016	Updated Appendix 1.
11/11/2016	Updated Appendix 1.
9/23/2016	Updated Appendix 1.
9/9/2016	Select Utah plans are now included in the site of care review.
7/15/2016	Updated formatting of policy, added additional medical rationale for potential waivers to policy, noted distinction between approved and unapproved hospital outpatient settings, clarified affected members, and updated references.

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Medication Policy Manual

Policy No: dru426

Topic: Enzyme Replacement Therapies

- Aldurazyme, laronidase
- carglumic acid (generic, Carbaglu)
- Elaprase, idursulfase
- Kanuma, sebelipase alfa
- Lamzede, velmanase alfa-tycv
- Lumizyme, alglucosidase alfa
- Mepsevii, vestronidase alfa
- Naglazyme, galsulfase
- Nexviazyme, avalglucosidase alfa
- nitisinone (generic, Orfadin, Nityr)
- Opfolda, miglustat
- Pombiliti, cipaglucosidase alfa
- Revcovi, elapegademase-lvlr
- Ryplazim, plasminogen, human-tvmb
- Sucraid, sacrosidase
- Vimizim, elosulfase alfa
- Xenpozyme, olipudase alfa-rpcp

Committee Approval Date: June 20, 2024

Date of Origin: November 13, 2015

Effective Date: July 15, 2024

Next Review Date: 2025

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

The medications included in this policy are used to treat rare genetic conditions caused by the deficiency of a specific enzyme. The enzyme deficiencies result in metabolic disorders, which can be fatal if left untreated. The prevalence of these diseases is rare, with many of them affecting less than one in forty thousand people.

Policy/Criteria

Most contracts require pre-authorization approval of enzyme replacement therapies (ERT) prior to coverage.

I. Continuation of therapy (COT): ERT (as listed in *Table 1*) may be considered medically necessary for COT when full policy criteria below are met, including diagnostic criteria (at baseline), quantity limit, and reauthorization criteria.

II. New starts (treatment-naïve) patients: ERT (as listed in *Table 1*) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A through D below are met.

A. There is documentation that confirms the medication is being used for its FDA-approved indication (as detailed in *Table 1*).

AND

B. The diagnosis has been established by or in conjunction with a specialist AND diagnostic criteria are met (as detailed in *Table 1*).

AND

C. Step therapy (if applicable for the ERT, as detailed in *Table 1*) has been ineffective, contraindicated, or not tolerated.

AND

D. For the provider administered ERT medications only (as applicable): Site of care administration requirements are met [refer to Medication Policy Manual, Site of Care (SOC) Review, dru408].

PLEASE NOTE: Not all medications in this policy are not part of the SOC program. Verify with the posted SOC policy.

Table 1. FDA Approved Indication, Specialist and Diagnostic Requirements, and Route of Administration			
Product	**Criteria II.A. FDA-approved Indication(s)**	**Criteria II.B. Specialist, Diagnostic Requirements** **Criteria II.C. Step Therapy Requirements**	**Route**
Injectable, Provider-administered			
Aldurazyme (laronidase)	MPS I (Hurler, Scheie, and Hurler-Scheie forms)	Medical genetics or metabolic specialist **AND** genetic and/or enzymatic confirmation (alpha-L-iduronidase deficiency).	IV, Provider
Elaprase (idursulfase)	MPS II (Hunter Syndrome)	Medical genetics or metabolic specialist **AND** genetic and/or enzymatic confirmation of MPS II (deficiency of I2S).	IV, Provider
Kanuma (sebelipase alfa)	Lysosomal acid lipase (LAL) deficiency	Endocrinologist, metabolic specialist, or medical geneticist/genetic specialist **AND** enzymatic confirmation (low/absent LAL levels).	IV, Provider
Lamzede (velmanase alfa-tycv)	Alpha-mannosidosis (AM)	Medical geneticist or metabolic specialist AND genetic and/or enzyme deficiency confirmation (<10% activity of alpha mannosidase enzyme).	IV, Provider
Lumizyme (alglucosidase alfa)	Pompe disease [acid α-glucosidase (GAA) deficiency]	Cardiology, medical genetics, or metabolic specialist **AND** genetic and/or enzymatic confirmation (GAA deficiency).	IV, Provider
Mepsevii (vestronidase alfa)	MPS VII (Sly syndrome)	Medical geneticist/genetic specialist **AND** enzymatic and/or genetic confirmation of MPS VII.	IV, Provider
Naglazyme (galsulfase)	MPS VI (Maroteaux-Lamy syndrome)	Medical genetics or metabolic specialist **AND** genetic and/or enzymatic confirmation (ASB deficiency).	IV, Provider
Nexviazyme (avalglucosidase alfa)	Late-onset Pompe disease (LOPD; GAA deficiency) in patients 1 year of age and older	Cardiology, medical genetics, or metabolic specialist **AND** genetic and/or enzymatic confirmation (GAA deficiency) **AND** (*in patients less than 30 kg ONLY*): treatment with Lumizyme (alglucosidase alfa) has been ineffective, contraindicated, or not tolerated.	IV, Provider

Table 1. FDA Approved Indication, Specialist and Diagnostic Requirements, and Route of Administration			
Product	**Criteria II.A. FDA-approved Indication(s)**	**Criteria II.B. Specialist, Diagnostic Requirements** **Criteria II.C. Step Therapy Requirements**	**Route**
Pombiliti (cipaglucosidase alfa)	In combination with Opfolda (miglustat) for late-onset Pompe disease (LOPD, GAA deficiency), in patients that are not improving on current ERT.	Cardiology, medical genetics, or metabolic specialist **AND** genetic and/or enzymatic confirmation (GAA deficiency) **AND T**reatment with Lumizyme (alglucosidase alfa) or Nexviazyme (avalglucosidase alfa) has been ineffective, contraindicated or not tolerated	IV, Provider
Revcovi (elapegademase-lvlr)	Adenosine deaminase severe combined immune deficiency (ADA-SCID)	Immunology or medical genetics **AND** genetic confirmation of ADA-SCID.	IV, Provider
Vimizim (elosulfase alfa)	Mucopolysaccharidosis (MPS) type IVA (Morquio A syndrome)	Medical genetics or metabolic specialist **AND** genetic and/or enzymatic confirmation (GALNS deficiency).	IM, Provider
Xenpozyme (olipudase-rpcp)	Non-central nervous system (non-CNS) manifestations of acid sphingomyelinase deficiency (ASMD)	Medical genetics or metabolic specialist **AND** genetic presence of SMPD1 mutation and/or enzymatic confirmation (acid sphingomyelin deficiency) **AND** documentation of non-CNS manifestations of ASMD (as defined in *Appendix 1).*	IV Provider
Provider-administered =OR= Self-administered ERT			
Ryplazim (plasminogen, human-tvmb)	Plasminogen deficiency (PLGD) type 1 (hypoplasminogenemia)	Dermatology, rheumatology, hematology, metabolic genetics, or metabolic specialist **AND** genetic confirmation of PLGD.	IV; Provider or self
Opfolda (miglustat)	In combination with Pombiliti (cipaglucosidase alfa) for late-onset Pompe disease (LOPD, GAA deficiency), in patients that are not improving on current	Cardiology, medical genetics, or metabolic specialist **AND** genetic and/or enzymatic confirmation (GAA deficiency) **AND** Treatment with Lumizyme (alglucosidase alfa) or Nexviazyme (avalglucosidase alfa) has been ineffective, contraindicated or not tolerated.	Oral; provider or self

Table 1. FDA Approved Indication, Specialist and Diagnostic Requirements, and Route of Administration			
Product	**Criteria II.A. FDA-approved Indication(s)**	**Criteria II.B. Specialist, Diagnostic Requirements** **Criteria II.C. Step Therapy Requirements**	**Route**
	ERT.		
Oral, Self-administered ERT			
Carglumic acid (generic, Carbaglu)	- Hyperammonemia due to N-acetylglutamate synthase (NAGS) deficiency, acute or chronic - Adjunctive therapy to standard of care for the treatment of acute hyperammonemia due to propionic acidemia (PA) or methylmalonic acidemia (MMA)	Medical genetics, or metabolic specialist. **AND** (*for NAGS only*) genetic confirmation of NAGS. **AND** (*for Brand Carbaglu*) Treatment with generic carglumic acid has been ineffective, contraindicated, or not tolerated.	Oral, self
Nitisinone (generic, Orfadin, Nityr)	Hereditary tyrosinemia type 1 (HT-1)	Medical genetics or metabolic specialist **AND** biochemical confirmation (presence of succinylacetone in the urine or plasma) **AND** treatment with generic nitisinone has been ineffective, contraindicated, or not tolerated (such as in patients unable to swallow generic capsules).	Oral, self
Sucraid (sacrosidase)	Congenital sucrose-isomaltase deficiency (CSID)	Gastroenterologist, endocrinologist, metabolic specialist, or medical genetics **AND** biochemical confirmation (low/absent sucrase activity on small bowel biopsy Note: Sucrase activity is considered abnormal when it is below the 10th percentile (<25 U per gram of protein, or <25 μM of sucrose converted per minute per gram of protein).	Oral, self

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers oral ERTs (as listed in *Table 1*, except Opfolda [miglustat]) coverable only under the pharmacy benefit (as self-administered medications).

B. Regence Pharmacy Services considers injectable ERTs [as listed in *Table 1*, except Ryplazim (plasminogen, human-tvmb)] coverable only under the medical benefit (as provider-administered medications).

C. Regence Pharmacy Services considers Ryplazim (plasminogen, human-tvmb) and Opfolda (miglustat) coverable under the pharmacy benefit (as a self-administered medication) OR coverable under the medical benefit (as a provider-administered medication).

D. When pre-authorization is approved, the ERT will be authorized using the following dosing schedules in *Table 2* below, using a current documented patient weight:

Table 2: ERT Quantity Limits (QL)

Product	Dosing schedule
Provider Administered	
Lumizyme (alglucosidase alfa)	Up to 26 IV infusions per year; ≤ 20 mg/kg every two weeks.
Nexviazyme (avalglucosidase alfa)	*Patients weighing 30 kg or more:* Up to 26 IV infusions per year; ≤ 20 mg/kg every two weeks. *Patients weighing less than 30 kg:* Up to 26 IV infusions per year; ≤ 40 mg/kg every two weeks.
Pombiliti (cipaglucosidase alfa)	Up to 26 IV infusions per year; ≤ 20 mg/kg every two weeks. **Please note:** Pombiliti (cipaglucosidase alfa) must be administered in combination with Opfolda (miglustat).
Revcovi (elapegademase-lvlr)	Up to 104 intramuscular injections per year.
Vimizim (elosulfase alfa)	Up to 52 IV infusions per year; ≤ 2 mg/kg every week.
Naglazyme (galsulfase)	Up to 52 IV infusions per year; ≤ 1 mg/kg every week.
Elaprase (idursulfase)	Up to 52 IV infusions per year; ≤ 0.5 mg/kg every week.
Aldurazyme (laronidase)	Up to 52 IV infusions per year; ≤ 0.58 mg/kg every week.
Xenpozyme (olipudase alfa-rpcp)	Up to 26 IV infusions per year, ≤ 3 mg/kg every 2 weeks.
Ryplazim (plasminogen, human-tvmb)	Up to 162 IV infusions per year; 6.6 mg/kg every 2 to 4 days.

Product	Dosing schedule
Kanuma (sebelipase alfa)	*Patients presenting in the first 6 months of life:* Up to 52 IV infusions per year; 5 mg/kg every week. *Adult and pediatric patients presenting after the first 6 months of life:* Up to 26 IV infusions per year, as follows: - Initial dosing: up to 1 mg/kg every two weeks. - For documented persistent symptoms (such as poor growth, liver/lipid abnormalities; See *Clinical Efficacy* section for details): up to 3 mg/kg every two weeks.
Lamzede (velmanase alfa-tycv)	Up to 52 IV infusions per year; ≤1 mg/kg every week.
Mepsevii (vestronidase alfa)	Up to 26 IV infusions per year; ≤ 4 mg/kg every two weeks.
Oral, self-administered	
Carglumic acid (generic, Carbaglu)	*Hyperammonemia due to NAGS Deficiency:* - Acute: 100-250 mg/kg/day by mouth, for up to 30 days; adjust dose to maintain normal plasma ammonia levels. After 30 days, chronic QL applies. - Chronic: 10-100 mg/kg/day by mouth; adjust dose to maintain normal plasma ammonia. - Authorization will be for up to 1 year. *Hyperammonemia due to PA or MMA – acute management* - ≤15 kg: 150 mg/kg/day, for up to 7 days. - >15 kg: 3.3 g/m^2 /day, for up to 7 days. - Coverable until ammonia level is less than 50 micromol/L, for up to a maximum duration of 7 days.
Nitisinone (Orfadin, Nityr)	- Initial dosing: Up to 1 mg/kg/day, by mouth. - For persistent succinylacetone in serum and/or urine: Up to 2 mg/kg/day, by mouth. - Authorization will be for up to 1 year.
Opfolda 65 mg capsule, (miglustat)	- Up to eight of the 65 mg capsules per 28 days. - Authorization will be for up to 1 year. **Please note:** Opfolda (miglustat) must be administered in combination with Pombiliti (cipaglucosidase alfa) and can be provider administered also
Sucraid (sacrosidase)	- ≤15 kg: 1mL per meal or snack, by mouth. - >15 kg: 2mL per meal or snack, by mouth. - Authorization will be for up to 1 year.

E. Authorization **shall** be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement, the patient is on the lowest effective dose, and a current weight, verified with clinical documentation such as a chart note from a clinic visit or a nurse infusion record. Criteria must be met for any dose escalation (as detailed in *Table 2*).

IV. The ERT included in this policy are considered investigational when used for any condition other than their FDA approved indications and when used in quantities greater than those listed above (in *Table 2*).

Position Statement

- The intent of this policy is to limit coverage of enzyme replacement therapies (ERTs, as listed in *Table 1*) in the diseases for and up to the doses for which they have been shown to be safe and effective in trials. The diagnosis for each product must have been established by a specialist in the given disease state.
- Only approximately half of the ERTs in this policy have safety and efficacy evidence from randomized, controlled trials to support use in their FDA approved indications (as detailed in the Clinical Efficacy below). The FDA approvals of the other ERTs were based on data from small, lower-quality, non-randomized trials. The medications included in this policy replace or replenish the deficient enzyme related to their respective FDA-approved indication and are the only pharmacologic treatment options available that treat the underlying cause of the disease.
- Drugs included in the policy are indicated for rare conditions for which a specialist is needed to confirm the diagnosis. Extensive diagnostic testing, including genetic testing or specialized laboratory testing, is required to confirm the diagnosis in most cases. In the absence of documented diagnostic testing, the associated therapies are not coverable.
- When lower cost options are available for a given disease, the higher cost ERT is coverable only when the lower cost ERT is not a treatment option.
    * In patients with late-onset Pompe disease who weigh 30 kg or less, Lumizyme (alglucosidase alfa) provides the best value to members. In patients weighing less than 30 kg, Nexviazyme (avalglucosidase alfa) is dosed two times higher has a longer infusion time and is significantly more costly than Lumizyme (alglucosidase alfa). Therefore, Nexviazyme (avalglucosidase alfa) is coverable only when Lumizyme (alglucosidase alfa) if not a treatment option.
    * Among the ERTs with generics, the branded formulations are coverable only when the less costly generic formulations are not an option. Current available generic formulations include generic carglumic acid and generic nitisinone.

- Guidelines for the use of ERTs for the treatment of these rare diseases (where available) generally align with the labeled use and coverage criteria, and may include use of other therapies, when feasible.
- Efficacy and safety of ERT doses exceeding the maximum dosage in the FDA-labeling have not been established in clinical trials.
- Efficacy and safety in other conditions (those not included in the FDA-labeling) have not been established in clinical trials.
- There is little potential for off-label use of these ERTs; however, the extremely high treatment costs, warrant confirmation of use for their FDA approved indications only.

Clinical Efficacy

Pompe Disease

- Pompe disease is an inherited disease caused by the deficiency or lack of the enzyme acid alpha-glucosidase (GAA), which is essential for normal muscle development and function. Damage to muscle is irreversible and patients die of respiratory failure. There are two phenotypes of Pompe disease, based on endogenous enzyme activity: [1]
    * Infantile onset Pompe disease (IOPD): no, or very low endogenous enzyme activity, onset early in life, progresses rapidly. Cardiac symptoms predominate, followed by respiratory failure. IOPD is almost always fatal before 1 year of age.
    * Late onset Pompe disease (LOPD): at least a small amount of residual GAA activity (< 40% normal), onset later in life (> 12 mo), slower disease progression. Respiratory symptoms predominate, due to progressive muscle weakness leading to gait disturbances and eventually die from respiratory failure.
- Lumizyme (alglucosidase alfa) is indicated for patients with Pompe disease. It was previously marketed as Myozyme (alglucosidase alfa) by the same manufacturer. The two formulations differ in the bioreactor used for production but not in pharmacologic effect.
- Lumizyme (alglucosidase alfa) has been shown to improve ventilator-free survival in patients with infantile-onset Pompe disease (IOPD), compared to an untreated historical control. Three open-label controlled studies evaluated alglucosidase alfa in 57 treatment naïve patients aged 0.2 months to 3.5 years with IOPD treated for 52-104 weeks. [2 3]
    * Primary outcomes assessed were death and need for invasive ventilator support.
    * All studies demonstrated a significant survival benefit compared to historical controls.
    * The precision of the study results is uncertain due to the absence of a control group in two of the studies, and the use of a historical control group in one of the studies.
- One high-quality systematic review of the available controlled trial evidence evaluated the use of alglucosidase alfa in patients with IOPD. Only one small randomized controlled trial (n=18) met inclusion criteria.[4]
    * The trial compared two dosing regimens (20 mg/kg every two weeks and the 40 mg/kg every two weeks) over 52 weeks, with a long-term extension to three years. There was no clear difference between the higher and lower doses for clinical

outcomes of cardiac function, motor development, proportion of children free of invasive ventilation; however, long-term use of alglucosidase alfa was effective for IOPD, with improvement of ventilator-free and overall survival, as well as for cardiac dysfunction.

* The review noted that there is a comparative lack of evidence to precisely conclude benefit of Lumizyme (alglucosidase alfa) for IOPD.
* Of note, the pivotal trial for the FDA approval of alglucosidase alfa in IOPD was excluded from the systematic review, given the lack of comparator arm.

- One high-quality systematic review of 19 randomized and observational studies evaluated the use of alglucosidase alfa in a total of 438 patients with late-onset Pompe disease (LOPD). [5]
  * Outcomes of interest were mortality, percent predicted forced vital capacity (% FVC), the 6-min walk test (6MWT), and ventilator use.
  * The top four outcomes with the most data included reduction in mortality, increased motor performance as measured by the six-minute walk test, improved respiratory status as measured by forced vital capacity, and the reduction in need for ventilator support (n=66).
  * With alglucosidase alfa therapy:
    - Mortality was lower (5-fold) [reported in most studies].
    - Respiratory function did not deteriorate as rapidly. FVC initially increased, then fell to baseline. However, FVC was higher relative to the loss seen in untreated patients with LOPD [n=298 in 11 studies].
    - 6MWT improved over the first 20 months, then stabilized over the following years, whereas 6MWT did not improve in untreated patients. [n=201 in 8 studies].
    - Ambulation status and the need for ventilator support was reported in 12 and 13 studies, respectively. However, quantification of treatment effect is not reliable due to heterogeneity of the available data.
  * RCTs, extension trials, single-arm trials, and observation trials (prospective and retrospective) were included. Only one trial of the 19 included was a randomized controlled trial.
  * Similar to previous meta-analyses,[6] the studies included in the review were of low quality as study populations were small (n<90), most studies evaluated surrogate endpoints, and retrospective studies were included in the systematic review (case series, uncontrolled single-arm trials, observational studies, and statistical analyses) undermining the certainty in the evidence of clinical benefit.
- Nexviazyme (avalglucosidase alfa) is indicated for patients 1 year of age or older with late-onset Pompe disease (LOPD). [7]
- It is not indicated for infantile-onset Pompe disease (IOPD).
- Nexviazyme (avalglucosidase alfa) was non-inferior to Lumizyme (alglucosidase alfa) in patients with LOPD, based on one randomized controlled study (n=100). [7]

    * Patients were randomized to Nexviazyme (avalglucosidase alfa) versus Lumizyme (alglucosidase alfa).
    * All patients were 1 year of age or older.
    * Results showed that Nexviazyme (avalglucosidase alfa) was non-inferior for the primary endpoint of change in predicted forced vital capacity (FVC).
- Pombiliti (cipaglucosidase alfa) in combination with Opfolda (miglustat) is indicated for the treatment of adults with late-onset Pompe disease (LOPD), who are not improving on their current ERT.[8 9]
- Pombiliti (cipaglucosidase alfa) with Opfolda (miglustat) is not indicated for IOPD.
- Pombiliti (cipaglucosidase alfa) with Opfolda (miglustat) demonstrated improvements in six-minute walk test (6-MWT) and pulmonary function (FVC) compared to alglucosidase alfa within the subset of ERT experienced patients in one small phase 3 randomized, double blind comparator trial (PROPEL, n=123).[10 11]
    * Patients were randomized 2:1 to Pombiliti (cipaglucosidase alfa) with Opfolda (miglustat) versus alglucosidase alfa with placebo.
    * Patients were 18 years of age or older having confirmed LOPD with 77% of patients being ERT experienced.
    * The primary endpoint was change from baseline in 6-MWT at 52 weeks, with a change of 5 meters that favored Pombiliti (cipaglucosidase alfa) plus Opfolda (miglustat) across the entire trial population, however the result was not significant (p=0.608).
    * Post-hoc analysis that excluded one extreme outlier in the alglucosidase alfa arm reported a change of 14 meters, which was still not significant (p=0.10) but considered clinically meaningful by the FDA.
    * In addition, subgroup analysis reported a significant difference of 16 meters favoring Pombiliti (cipaglucosidase alfa) with Opfolda (miglustat) in patients that were ERT experienced (P=0.047).
    * The key secondary endpoint of change from baseline in FVC across all participants was 2.3% (p=0.05) significantly favoring of Pombiliti (cipaglucosidase alfa) with Opfolda (miglustat).
- Use of Pombiliti in combination with Opfolda (miglustat) will therefore only be authorized in patients with LOPD who are not improving on their current ERT, in accordance with the FDA labeled indication.
- Due to small sample size in the ERT naïve patient population, conclusions were not able to be drawn in regard to efficacy, therefore use in this patient population is considered investigational.
- The use of Pombiliti (cipaglucosidase alfa) with Opfolda (miglustat) in IOPD or in combination with other ERT's has not been studied and use will also be considered investigational.
- Miglustat (generic, Zavesca) had previously been approved for use in Gaucher disease, however the indication, dosage, and frequency differs from that of Opfolda (miglustat).[10]

- Therefore, the use of Opfolda (miglustat) in any other indication outside of the coverage criteria outlined above will be considered investigational, and use of miglustat (generic, Zavesca) in LOPD will also be considered investigational.
- Dose escalation: There is interest in the use of higher doses of ERT in both early and late onset Pompe disease (IOPD, LOPD). However, there is insufficient evidence at this time to conclude additional benefit from higher doses of Lumizyme (alglucosidase alfa), in excess of 20 mg/kg every 2 weeks. The available evidence is limited to various case reports and retrospective analyses, as well as one exploratory trial. [12-14]
- An open label exploratory trial (2015) randomized 13 patients to standard versus escalated dose alglucosidase alfa (20 mg/kg/week or 40 mg/kg/2 weeks). [12]The authors concluded there may be some benefit of higher ERT dosing in some patients with motor decline. However, larger, controlled trials are needed to establish a superior efficacy, as well as risks, of higher doses of ERT in patients with Pompe disease.
- A 2020 retrospective review of patients with IPD (n=7) and LOPD (n=4) and dose escalation observed benefit from higher doses of Lumizyme (alglucosidase alfa) (40 mg/kg weekly). However, given the absence of a comparator arm and the retrospective, uncontrolled nature of the trial, conclusion of a relative benefit of higher dosing of Lumizyme (alglucosidase alfa) is not possible. [13]
- More recently (2022), a multicentre observational cohort study report various outcomes with a variety of Lumizyme (alglucosidase alfa) dosing strategies (39 dosing regimens in 124 patients). [14] There was a non-statistically significant difference between standard dosage (20 mg/kg every other week), intermediate dosage (20 mg/kg per week, or higher 40 mg/kg every other week), and high dosage (40 mg/kg per week) for health outcomes, such as walking. Therefore, the use of Lumizyme (alglucosidase alfa) in doses of more than 20 mg/kg per week is considered investigational, with an unproven health outcome from higher dosing.

  Guidelines: Based on the available evidence and consensus recommendations of specialists, guidelines for the treatment of late-onset Pompe disease recommend: [1 15]
- Initiating treatment with ERT at the onset of symptoms and to re-evaluate annually to reassess whether treatment should continue.
- Newborn genetic screening is recommended, along with leukocyte GAA enzyme activity, to confirm a diagnosis of Pompe.

Carglumic acid (generic, Carbaglu) for NAGS, PA, and MMA

- Carglumic acid is indicated for the following diagnoses, to normalize ammonia levels: [16]
  * Adjunctive therapy for the treatment of acute hyperammonemia due to the deficiency of hepatic enzyme N-acetylglutamate synthase (NAGS).
  * For maintenance therapy for the treatment of chronic hyperammonemia due to the deficiency of the hepatic enzyme NAGS.
  * Adjunctive therapy to standard of care for the acute treatment of hyperammonemia due to propionic acidemia (PA) or methylmalonic acidemia (MMA).
- FDA approval of carglumic acid for NAGS was based on a retrospective, unblinded, and uncontrolled review of patients with NAGS deficiency. Short-term impact on plasma

ammonia levels was evaluated in 23 patients over three days, while long-term impact was evaluated in 13 patients over a mean length of 8 years (range 1 to 16 years). [16]

  * After 3 days, mean ammonia levels dropped from 157 umol/L to 27 umol/L.
  * After a mean of 6 years, the mean ammonia level was 23 umol/L in 13 patients.
  * Acute hyperammonemia was controlled in all patients by Day 3. Therefore, higher doses of carglumic acid (up to 250 mg/kg/day) for acute hyperammonemia is coverable for a maximum of 30 days, after which time chronic dosing (up to 100 mg/kg/day) is coverable as maintenance therapy.

- Subsequently, approval for PA or MMA was based on a randomized, controlled trial in patients with genetically confirmed late-onset CPS1 deficiency (CPSD) and late-onset Ornithine transcarbamylase deficiency (OTCD), for acute hyperammonemia. [16]
  * All patients received standard of care therapy, including a combination of protein restriction, intravenous glucose, insulin, and/or L-carnitine.
  * All patients had a baseline ammonia level of ≥ 70 mmol/L. carglumic acid was given until ammonia level was ≤ 50 mmol/L, or until hospital discharge, up to a maximum of 7 days.
  * Addition of carglumic acid to standard treatment resulted in a more rapid normalization of plasma ammonia levels compared to placebo, administered for a maximum of seven days.
- NAGS, PA, and MMA are extremely rare conditions and evidence-based treatment guidelines are not available. However, genetic testing is required to definitively diagnosis NAGS, CPSD, and OTCD, an inherited autosomal recessive disorders. [17]

Revcovi (elapegademase-lvlr)for ADA-SCID [18 19]

- Elapegademase is indicated in patients with adenosine deaminase severe combined immunodeficiency (ADA-SCID). ADA-SCID is a rare, inherited condition caused by a lack of functional ADA, which results in severe T-lymphopenia.
- Efficacy was demonstrated in two small studies in a total of ten patients. The studies demonstrated that elapegademase is able to improve of serum adenosine deaminase activity and immune status while reducing the concentration of toxic metabolites. Improvements in these measures have been associated with long-term survival. [19]
- The diagnosis of ADA-SCID is confirmed by genetic testing (bi-allelic mutations in the ADA gene), to confirm ADA deficiency. Hematopoietic stem cell transplant (HSCT) is the definitive treatment for ADA-SCID. Guidelines for recommend ERT in patients who are not candidates for a bone marrow transplant or if gene therapy is not available (Note: gene therapy for ADA-SCID is not currently available in the US). [20]

Nitisinone (Orfadin, Nityr) for HT-1

- Nitisinone is indicated as an adjunct to dietary restriction of tyrosine and phenylalanine in the treatment of hereditary tyrosinemia type 1 (HT-1), an autosomal recessive genetic condition characterized by progressive liver disease and renal tubular dysfunction. [21 22]
- Nitisinone is available as a less costly generic, as a 2 mg, 5 mg, and 10 mg capsule, relative to the branded formulations of nitisinone (Orfadin, Nityr). Only branded nitisinone (Orfadin) is available as an oral suspension and is therefore coverable for

patients unable to swallow generic capsules.

- Efficacy of nitisinone, in combination with dietary controls, was established in one open-label, uncontrolled study of 207 patients with HT-1, aged 0 to 21.7 years old. [22]
    * Efficacy was assessed by comparison of survival and incidence liver transplant relative to historical controls.
    * The median duration of treatment was 22 months.
    * For patients ≤ 2 years of age, the 2- and 4- year survival probabilities were 88%. Patients ≤ 2 years of age who had been treated with dietary restriction alone had 2- and 4- year survival probabilities of 29%.
    * For patients presenting between 2 and 6 years of age, 2- and 4-year survival probabilities were 94%. Patients between 2 and 6 years of age who had been treated with dietary restriction alone had 2- and 4-year survival probabilities of 74% and 60%, respectively.
- Evidence-based treatment guidelines are not available for HT-1. However, based on standard of care as well as the available clinical trials of nitisinone: [22 23]
    * HT-1 is diagnosed by presence of by the presence of succinylacetone in the urine or plasma. Genetic testing for the autosomal recessive trait is available, but not required for diagnosis of HT-1.
    * Patients are typically managed through dietary restriction of protein. Nitisinone is considered the treatment of choice, as the only pharmacotherapy that can limit the formation of toxic compounds present in HT-1. Dosing is initiated at 1 mg/kg/day. The dose may be titrated based on biochemical and/or clinical response to a maximum of 2 mg/kg/day, such as based on serum and/or urine succinylacetone levels.
    * Liver transplantation is considered an option for patients who do not respond to nitisinone.
- *INVESTIGATIONAL USES*: One clinical trial evaluated the efficacy of nitisinone in alkaptonuria, an off-label use. While some clinical trials had shown that nitisinone was effective in reducing urinary homogentisic acid, a confirmatory randomized trial was conducted to evaluate clinical benefit in patients with alkaptonuria. At the end of the 36-month evaluation period, no benefit was observed in primary or secondary parameters. Measures of clinical efficacy included change in total range of motion in the worse hip, change in spinal flexion, 6-minute walk times, and functional reach. [24]

Xenpozyme (olipudase alfa-rpcp) for ASMD

- Xenpozyme (olipudase alfa-rpcp) is indicated for the treatment of non-central nervous system (non-CNS) manifestations of acid sphingomyelinase deficiency (ASMD) in adult and pediatric patients.[25]
- ASMD, historically known as Niemann-Pick disease A and B, is characterized by a deficiency in the acid sphingomyelin enzyme, due to a mutation in the SMPD1 gene. The deficiency leads to a buildup of sphingomyelin in multiple major organ systems, causing CNS neurodegeneration, hepatosplenomegaly, lung alterations, thrombocytopenia, lipid abnormalities, short stature, and osteopenia.[26]

- ASMD is considered a disease spectrum that is divided based on onset, clinical presentation, severity, and rate of progression described below:[27]
    * Type A: most severe form with infant onset, presents with rapidly progressing neurodegeneration, hepatosplenomegaly, and pathologic alterations in lungs; often fatal by age 3 due to respiratory failure.
    * Type B: later onset with less severe disease, manifests with hepatosplenomegaly and lung alterations, but no CNS involvement; patients frequently live into adulthood.
    * Type A/B: an intermediated form with presentation and progression rate varying greatly but most have some CNS symptoms.
- Efficacy of Xenpozyme (olipudase alfa-rpcp) in adults was established in the ASCEND trial (n=31), a phase 2/3 randomized, double blind placebo-controlled trial in patients with type B or type A/B confirmed ASMD.[26 28]
    * Patients aged 18-66, were randomized to Xenpozyme (olipudase alfa-rpcp) titrated up to 3 mg/kg every two weeks or placebo for 52 weeks.[26]
    * All patients had the diagnosis confirmed with a documented deficiency of ASM, defined by either enzyme assay and/or genotyping.
    * Patients with type A were excluded from the trial.
    * There were two primary efficacy outcomes, the first being the mean percent change from baseline in diffusing capacity of the lung for carbon monoxide (DL_{co}), a validated clinical tool used to measure progression in interstitial lung disease (ILD), which has never been used as an endpoint in a clinical trial and meaningful impact on quality of life or overall survival is unknown. [26]
    * The second primary endpoint was a composite endpoint of average percent change in spleen volume from baseline and a novel unvalidated patient reported outcome, the splenomegaly related score (SRS).[26]
    * Xenpozyme (olipudase alfa-rpcp) significantly improved DL_{co} and spleen volume compared to placebo (24.0 vs 2.98 and -38.8 vs 0.40, respectively), however there was no change in SRS quality of life measure. Secondary endpoints also showed statistical improvement in liver volume, additional pulmonary function markers, platelet count, and lipid panel.[28]
- Safety and efficacy of Xenpozyme (olipudase alfa-rpcp) in pediatric patients was established in the ASCEND-Peds trial (n=8), a phase 1/2 open label single arm trial in patients with confirmed type A/B or type B ASMD.[26 29]
    * Patients aged 1-12 received Xenpozyme (olipudase alfa-rpcp) titrated up to 3 mg/kg every two weeks for 64 weeks.
    * Trial design was to evaluate safety and tolerability of Xenpozyme (olipudase alfa-rpcp), and the efficacy endpoints were exploratory.
    * Xenpozyme (olipudase alfa-rpcp) demonstrated similar efficacy shown in the ASECND adult population with improvement in mean percent change from baseline of lung function, hepatosplenomegaly, and thrombocytopenia, however these results are from an extremely small sample size and true efficacy is unknown.[26]

- FDA approval was based on the results from the trials above showing improvements in DL_{CO}, spleen volume, liver volume as well as pharmacodynamic biomarker results of a consistent reduction of sphingomyelin in the trials when compared to placebo. Clinically meaningful benefit, such as survival, improvement in quality of life or disease burden has yet to be demonstrated.
- No treatment guidelines for ASMD are available and there are no treatment alternatives. Xenpozyme (olipudase alfa-rpcp) is the only FDA-approved treatment. Documentation of acid sphingomyelin enzyme deficiency or presence of a SMPD1 gene mutation was required for trial entry and is considered diagnostic for ASMD.[27]
- Xenpozyme (olipudase alfa-rpcp) does not cross the blood brain barrier, therefore it is not FDA approved to treat CNS manifestations for ASMD.[26] The use of Xenpozyme (olipudase alfa) is limited to patients presenting with non-CNS manifestations of ASMD. Use of Xenpozyme (olipudase alfa-rpcp) in patients presenting with only CNS symptoms is considered investigational.

Ryplazim (plasminogen, human-tvmb) for PLGD [30-32]

- Ryplazim (plasminogen, human-tvmb) in indicated for the treatment of patients with plasminogen deficiency (PLGD) type 1.
- PLGD is characterized by the development of thick growths, or lesions, throughout the body that may be painful and can cause severe and potentially life-threatening complications. These lesions are caused by inflammation and the deposition of fibrin. Ryplazim (plasminogen, human-tvmb) acts as replacement plasminogen therapy, which allows for the clearance of fibrin.
- Approval of plasminogen was based on a single-arm, open-label phase 2/3 study in 15 patients with genetically-confirmed PLGD with biallelic mutations in the plasminogen (PLG) gene. Treatment with plasminogen normalized plasminogen levels and improved lesion size and severity.
- There is currently no screening test available for PLGD; molecular genetic testing can only confirm a diagnosis. Diagnosis relies on clinical symptoms, family medical history, and confirmatory testing.

Sucraid (sacrosidase) for CSID

- Sucrase-isomaltase deficiency can be congenital or acquired (often secondary to damage to the enteric brush border membrane from other chronic GI conditions such as celiac disease, Crohn's disease, and H. pylori).
- Sacrosidase is indicated for the treatment of *congenital* sucrose-isomaltase deficiency (CSID), also known as genetically determined sucrase deficiency. It is not intended for use in acquired sucrase-isomaltase deficiency.[33]
- CSID is a rare, genetic condition which impairs ability to digest sugars (sucrose and maltose). Patients with CSID have GI symptoms (stomach cramping, excessive gas, bloating, explosive diarrhea, vomiting) after ingestion of sugar. In infants, CSID may lead to malnutrition and failure to thrive. [34]
- CSID is caused by a mutation in the SI gene. The diagnosis of CSID is confirmed with a small intestinal biopsy, to confirm a deficiency of sucrase activity.

- Efficacy of sacrosidase in *congenital* sucrose-isomaltase deficiency was established in a randomized, double-blind, controlled trial consisting of two phases: 1) a comparative phase, evaluating placebo, sacrosidase, and sacrosidase plus milk and 2) a dose-response phase with various concentrations of sacrosidase. 28 patients aged 5 months to 11 years were enrolled. [33-35]
    * Criteria for inclusion were a history of chronic watery diarrhea with an acid pH, a small intestinal biopsy specimen with measurement of tissue disaccharidase levels showing sucrase activity of less than 10% of control specimens with normal lactase levels and normal or decreased maltase activity, normal villous architecture of the small intestine, and a normal result in a lactose breath hydrogen test.
    * Breath hydrogen excretion decreased significantly in patients receiving sacrosidase, with or without milk.
    * In the dose-response phase, higher concentrations of sacrosidase were associated with fewer stools and a greater number of formed or hard stools compared to baseline.
- A prior study of similar design evaluated different concentrations of sacrosidase in the dose-response phase in patients with *congenital* sucrose-isomaltase deficiency. (n=14). [33 36]
    * Diagnostic criteria for inclusion were similar (chronic watery diarrhea with an acid pH, a small intestinal biopsy specimen with measurement of tissue disaccharidase levels showing complete or near absence of sucrase activity, normal villous architecture of the small intestine, a normal lactose breath hydrogen test, and no other cause of chronic diarrhea).
    * Although the effective on stool-related outcomes were inconsistent with the subsequent trial, this trial supported the other trial finding that breath hydrogen excretion decreased significantly with sacrosidase.
- No treatment guidelines for CSID are available. However, a 2020 review of CSID diagnosis and management (sponsored by the manufacturer of Sucraid) affirmed that endoscopic small intestinal biopsy assayed for disaccharidase activity (usually lactase, maltase, isomaltase/palatinase, and sucrase) is the gold standard diagnostic to confirm a deficiency of sucrase activity, [37] along with a retrospective review of physician diagnostic practice [38] as well as the FDA Medical Review for Sucraid. [34] Sucrase levels greater than 25 U/g (uM/min/ g protein) are considered normal.[39 40] Less-invasive tests, such as breath testing, sucrose challenge, and use of a ERT (Sucraid) trial, may support a diagnosis of CSID, but are not confirmatory for the diagnosis and are prone to error. [41] Of note, the pivotal trials for the approval of Sucraid (sacrosidase) only enrolled patients with a history of chronic diarrhea and confirmation of CSID with intestinal biopsy. Therefore, the use of Sucraid (sacrosidase) in the absence of a biopsy-confirmed diagnosis of CSID is considered “not medically necessary.” Dietary restriction of sucrose, isomaltose, and maltose and enzyme replacement therapy with sacrosidase are the only available treatment options. Of note, negative genetic testing does not exclude the diagnosis of CSID. Therefore, genetic testing is not specifically recommended as standard of care. In addition, although growing evidence suggests disease in SI heterozygous or homozygous variants, these patients often have less severe

presentations and patients may be getting diagnosed later in life. Evidence for use of sacrosidase in these patients is lacking.

- There are no clinical trials to establish the safety and efficacy of sacrosidase in *acquired* sucrose-isomaltase deficiency, such as deficiency secondary to other chronic GI conditions such as celiac disease, Crohn's disease, and H. pylori.

Kanuma (sebelipase alfa) for lysosomal acid lipase (LAL) Deficiency

- Sebelipase alfa is indicated for the treatment of LAL deficiency in infants, pediatric patients, and adults. [42]
- Disease Background: [43 44]
    * LAL catalyzes breakdown of cholesterol esters and triglycerides within lysosomes of cells. Deficiency of LAL results in accumulation of cholesterol esters and triglycerides in vital tissues and organs.
    * The clinical severity depends on the severity of the LAL deficiency. Patients with little to no LAL activity typically present at 2 to 4 months and rarely survive to 12 months (median survival historically is ~ 1.3 months). Typical presentation is characterized by malabsorption, growth failure, and liver failure. Less severe LAL deficiencies present as a widely variable clinical course, with involvement of multiple organs, dyslipidemia, and liver disease as the most prominent feature. LAL deficiency may lead to hepatic steatosis, fibrosis, and progressive cirrhosis. Historically, patients were treated with HMG CoA-reductase inhibitors ("statins"). While improvements in serum lipids and hepatic steatosis have been shown, the effect on liver fibrosis or other clinical endpoints is not known.
- Efficacy of sebelipase alfa in infants presenting within the first 6 months of life was established in an open label phase 2/3 trial comparing survival in nine patients vs. historical controls (LAL-CL03; VITAL). [43 44]
    * Patients were treated with sebelipase alfa 0.35 mg/kg once weekly, with dose escalation to 1mg/kg. The trial protocol was later amended to allow escalation up to 5mg/kg, or every-other week infusions for stable patients. The initial FDA labeling allowed for up to 3 mg/kg once weekly.
    * Six of nine patients in the study group survived to 12 months of age vs. zero of 21 historical controls.
- A phase 3 study compared sebelipase alfa to placebo in pediatric and adult patients aged 4 to 58 years of age in a double-blind, placebo-controlled trial (LAL-CL02; ARISE). [45]
    * Patients were randomized to sebelipase alfa 1 mg/kg every two weeks or placebo.
    * The primary efficacy outcome was normalization of alanine amino transferase (ALT) levels. The FDA determined this endpoint was not clinically meaningful.
    * FDA approval was based on the secondary endpoint of reduction in LDL cholesterol levels. No clinically meaningful benefit, such as clinically meaningful endpoints such as survival, QOL, or disease burden, has been demonstrated.
- Long-term (5-year) survival data was published for three open-label extension trials, which allowed dose escalation in patients with a suboptimal clinical response. [46 47]
    * In children with onset within the first 6 months of life:

    - The trial enrolled patients who completed the phase 2/3 LAL-CL03/VITAL and 10 from the phase 2 LAL-CL08. Doses of Kanuma (sebelipase alfa) were escalated up to 5 mg/kg once weekly "at the discretion of the investigator" (4 of 19 patients).
    - Dose escalation was considered within the first three months for failure to grow (weight and height), low albumin, persistent ALT elevation, and ongoing transfusions. Beyond three months, additional dose escalation could be considered for persistent poor growth, low albumin, persistent ALT elevation, hepatomegaly, splenomegaly, or lymphadenopathy.
  * In pediatric and adult patients (CL04):
    - The trial enrolled patients who completed the phase 2 CL01 dose-escalation trial. Doses of Kanuma (sebelipase alfa) were escalated up to 3 mg/kg every other week (3 of 9 patients).
    - A suboptimal clinical response was defined as any of the following that did not improve from baseline or failed to normalize within 12 months: poor growth, deteriorating biochemical markers (such as liver function tests, lipid profile, liver biopsy), or persistent or worsening organomegaly (such as liver fibrosis/cirrhosis, splenomegaly).
  * The long-term extension trials found a survival benefit with use of Kanuma (sebelipase alfa). However, the number of patients on escalated doses was very small relative to the total treated patients, as well as the available phase 3 data. Therefore, the benefit of escalated dosing relative to lower dosing remains uncertain.
- No treatment guidelines for LAL deficiency are available. If the disease presents in the first year of life, it is rapidly fatal and there are no treatment alternatives. Disease that presents later in life has a varying clinical course. Sebelipase alfa is the only FDA-approved treatment. Documentation of LAL deficiency was required for sebelipase alfa trial entry and is considered diagnostic for LAL deficiency.

Lamzede (velmanase alfa-tycv) for AM

- Lamzede (velmanase alfa-tycv) is indicated for the treatment of non-central nervous system (non-CNS) manifestations of alpha-mannosidosis (AM) in adult and pediatric patients.[48]
- AM is characterized by a deficiency in the alpha mannosidase enzyme, due to mutations in the MAN2B1 gene. The deficiency leads to an accumulation of oligosaccharides in lysosomes that affect multiple organ systems, causing immune deficiency, skeletal abnormalities (scoliosis), distinctive facial features, pain, hearing and speech impairment, progressive impairment of mental function, muscular weakness leading to ataxia with most patients losing independence and requiring use of a wheelchair.[49]
- AM is considered a disease spectrum that may not be clearly distinguishable due to the broad heterogeneity of the disease and clinical manifestations.[49]
- Efficacy of Lamzede (velmanase alfa-tycv) was established in the rhLAMAN-05 trial (n=35), a phase 3 international, multicenter, randomized, double-blind, placebo-controlled trial in patients with AM.[50 51]

    * Patients aged 5-35 were randomized to Lamzede (velmanase alfa-tycv) at 1 mg/kg weekly or placebo for 52 weeks.
    * All patients had AM diagnosis confirmed via alpha mannosidase enzyme deficiency (defined as <10% enzyme activity).
    * All subtypes of AM could be included in trial with the only exclusion being unable to walk without support (however limited assistance or wheelchair use was allowed for long distances).
    * There were two primary efficacy outcomes, the first being the change from baseline at week 52 of the serum oligosaccharide concentration, an unvalidated surrogate marker that is thought to be physiologically relevant and is a disease specific biomarker, however its meaningful impact on quality of life or overall survival is unknown.
    * The second primary efficacy endpoint was change in baseline in the 3-minute stair climb test (3-MSCT), a surrogate endpoint used to measure functional activity that has previously been used in other enzyme replacement trials, but a minimal clinical important difference has yet to be determined.
    * Lamzede (velmanase alfa-tycv) significantly reduced the serum oligosaccharide concentration compared to placebo (-5.1 vs -1.6), while also improving 3-MSCT score from baseline (0.6 vs -2.4), although not significantly.
    * Secondary endpoints included change in baseline of forced vital capacity (a measure of lung function) as well as the six-minute walk test (6-MWT), a measure of daily functioning, both validated surrogate endpoints that favored treatment with Lamzede (velmanase alfa-tycv), but not significantly.
- FDA approval was based on the efficacy results from the rhLAMAN-05 trial showing a significant reduction in serum oligosaccharide concentration as well as improvement in pulmonary and mobility functional measures when compared to placebo, which was supported by results of smaller, phase 2 trials as well as a phase 3 integrated long term efficacy trial that all showed similar results to the primary trial.[50 52]
- However, these surrogate markers are not directly related to clinically meaningful benefit on outcomes such as improved overall survival, quality of life measures, or disease burden.
- No treatment guidelines for AM are available and there are no other treatment alternatives.[50]
- Documentation of alpha mannosidase enzyme deficiency (< 10%) was required for trial entry and is considered diagnostic for AM. MAN2B1 gene mutations are also considered diagnostic but were not required for trial entry.
- The use of Lamzede (velmanase alfa-tycv) for any other indication is considered investigational.

Mucopolysaccharidoses - types I II, III (A to D), IV (A or B), VI, VII, and IX [1 53]

- Mucopolysaccharidoses (MPS) are lysosomal storage disorders caused by the deficiency of enzymes required for the stepwise breakdown of glycosaminoglycans (GAGs). Fragments of partially degraded GAGs accumulate in the lysosomes, resulting in cellular dysfunction and clinical abnormalities.

- The MPS disorders are classified as types I II, III (A to D), IV (A or B), VI, VII, and IX. MPS V (formerly Scheie syndrome) and MPS VIII are no longer recognized. The MPS disorders are differentiated clinically by their clinical features and age of presentation and biochemically by their associated enzyme deficiency. They can be grouped into four broad categories according to their dominant clinical features:
    * Soft tissue storage and skeletal disease with or without brain disease (MPS I, II, VII)
    * Soft tissue and skeletal disease (MPS VI)
- Primarily skeletal disorders (MPS IV A and B)
    * Primarily CNS disorders (MPS III A to D)
- MPS affects many other systems and other complications of the disease including recurrent hernias (due to hepatosplenomegaly), chronic ear infections, chronic respiratory infections, poor vision, poor hearing, communicating hydrocephalus, and sleep apnea. Growth height is also significantly less than normal. [54]
- Demonstration of a specific enzyme deficiency, usually in peripheral blood leukocytes, although fibroblasts or dried blood spots, is needed for confirmation of diagnosis. Enzyme analysis is available for all types of MPS.
- FDA-approved ERT is available for: MPS I, II, IVA, VI, VII. ERT is generally used in patient with moderate to severe disease. ERT has only been shown to slow the progression of the disease.

Vimizim (elosulfase alfa) for MPS IVA

- Elosulfase alfa is indicated for patients with Mucopolysaccharidosis type IV A (MPS IVA; also known as Morquio A syndrome). [55] This condition affects roughly 1 per 100,000 individuals. Patients lack the enzyme N-acetylgalactosamine-6-sulfatase (GALNS), which results in skeletal abnormalities. [53] Symptoms may also include visual, splenic, cardiac, and auditory.
- FDA approval was based on a randomized, double-blind, placebo-controlled, trial of 176 patients with MPS IVA, ranging from 5 to 57 in age. Patients received elosulfase alfa or placebo. [55 56]
    * The primary end point was the change from baseline in the distance walked in six minutes (six-minute walk test, 6-MWT) at week 24.
    * The mean difference in 6-MWT between elosulfase alfa and placebo was 23 meters (95% CI 2.9, 43.1).
    * No additional improvement was observed in a 48-week follow-up extension study.
- Guidelines recommend initiating ERT as soon as the diagnosis has been confirmed by an enzyme activity test (reduced GALNS). Genetic testing may be used for confirmation. [57]

Naglazyme (galsulfase) for MPS VI

- Galsulfase is indicated for patients with Mucopolysaccharidosis VI (MPS VI; also known as Maroteaux-Lamy syndrome). This condition affects roughly 1 per 300,000 individuals.
- MPS VI is caused by mutation on the ARSB gene, which leads to a deficiency of the enzyme arylsulfatase B (ASB; N-acetylgalactosamine-4-sulfatase). The ASB deficiency results in skeletal deformities and respiratory difficulties, as well as cardiac abnormalities. [1 53 58]

- In a randomized, double-blind, placebo-controlled trial, 38 patients with MPS VI received galsulfase or placebo for 24 weeks. [59] Patients ranged in age from 5 to 29 years old.
    * The primary endpoint was the change from baseline in the distance walked in 12 minutes (12-minute walk test, 12-MWT).
    * Patients treated with galsulfase saw a greater difference in the 12-MWT than those treated with placebo (mean difference of 83 meters).
- Treatment guidelines recommend ERT with galsulfase as a first-line treatment option for patients with MPS VI, when the diagnosis has been confirmed by an enzyme activity test (reduced ASB). Genetic testing may be used for confirmation. [58]

Elaprase (idursulfase) for MPS II

- Idursulfase is indicated for patients with Mucopolysaccharidosis II (MPS II; also known as Hunter Syndrome). This condition affects roughly 1 per 150,000 individuals. [60]
- MPS II is caused by a deficiency of iduronate 2-sulfatase (I2S), due to mutations in the I2S gene, which results in various symptoms (coarse facial features, severe skeletal disease, joint abnormalities, respiratory disease, and cardiac abnormalities, obstructive sleep apnea and pulmonary hypertension, vision, and hearing disorders, and/or hydrocephalus).
- In a randomized, double-blind, placebo-controlled trial, 96 patients with MPS II received idursulfase or placebo for 53 weeks. Patients ranged in age from 5 to 31 years old. [61]
    * The primary endpoint was the change from baseline in the distance walked in 6 minutes (6-minute walk test, 6-MWT).
    * The mean difference in 6-MWT between idursulfase and placebo was 37 meters.
- Although evidence is limited in patients less than 5 years old, European guidelines recommend that ERT with idursulfase be initiated for any patient with a biochemically confirmed diagnosis of MPS II, including those younger than 5. [60]
- Treatment guidelines for Mucopolysaccharidoses II recommend idursulfase, as a first-line treatment options for patients with a confirmed diagnosis. Gold standard is documentation of iduronate 2-sulfatase (I2S) deficiency. Screening urinary glycosaminoglycans I diagnostic for MPS II with confirmation by measuring I2S activity and analyzing I2S gene mutations. [1 60 62]

Aldurazyme (laronidase) for MPS I

- Laronidase is indicated for patients with Mucopolysaccharidosis I (MPS I), specifically for Hurler and Hurler-Scheie forms of the disease, and for patients with the Scheie form who have moderate to severe symptoms.[63] MPS I is due to a gene mutation which leads to a deficiency of alpha-l-iduronidase (IDUA). Clinical manifestations include respiratory and cardiovascular complications, skeletal manifestations, arthropathy, loss of hearing and vision, gastrointestinal symptoms, and hydrocephalus. This condition affects roughly 1 per 100,000 individuals. [64]
- Approval was based on a randomized, double-blind, placebo-controlled trial in 45 patients, aged 6 to 43 years old. [65]

    * One patient had the Hurler form, 37 the Hurler-Scheie form, and 7 the Scheie form. Patients received laronidase or placebo for 26 weeks.
    * The primary endpoints were percent predicted forced vital capacity (FVC) and the change from baseline in the distance walked in 6 minutes (6-minute walk test, 6-MWT).
    * Respiratory and physical improvements were achieved in patients receiving laronidase.
    * The mean difference in % of predicted normal FVC was 4 (p=0.02); the mean difference in 6-MWT was 39 meters (p=0.07), comparing laronidase to placebo.
    * The improvement in percent predicted FVC and 6-MWT was maintained after 182 weeks, as evaluated in an open-label in a long-term extension study.
- Treatment guidelines for MPS I highlight the significance of individualized treatment based on the clinical picture of each patient. Enzymatic analysis [alpha-l-iduronidase (IDUA) deficiency] is diagnostic; however, genetic analysis is required for confirmation of phenotype, which is predictive of disease severity. Considerations such as needs patient age, developmental quotient, disease phenotype, severity of disease, and potential for growth should be evaluated before pursuing a hematopoietic stem cell transplant or ERT. [1 64]

Mepsevii (vestronidase alfa)for MPS VII

- Mepsevii (vestronidase alfa), (recombinant human beta-glucuronidase [rhGUS]), is indicated for the treatment of MPS VII (Sly syndrome) in pediatric and adult patients. [66] MPS VII is due to a gene mutation which leads to a deficiency of beta-glucuronidase.
- Patients with MPS VII experience significant development issues. Development slows by 1 to 3 years of age, which is then followed by a regression of skills until death. [54]
- Approval for Mepsevii (vestronidase alfa) was based on one phase 3, randomized, placebo-controlled trial in twelve patients with a diagnosis of MPS VII, based on leukocyte or fibroblast glucuronidase enzyme assay or genetic testing, as well as the clinical history of patients who received treatment with Mepsevii (vestronidase alfa) in phase 1 trials and expanded access programs [67] While the body of evidence for Mepsevii (vestronidase alfa) is of low quality due to the rarity of the condition and the nature of the disease, patients experienced improvement in several parameters that suggest clinical efficacy of the drug.
- No treatment guidelines for MPS VII (Sly syndrome) are available. Mepsevii (vestronidase alfa) is the only FDA-approved treatment. Diagnosis is confirmed with testing for enzyme levels (beta-glucuronidase deficiency). [53]

Safety

- ERTs for Pompe disease have black box warnings for anaphylactic reactions during infusions, and in patients with compromised cardiac or respiratory function, a risk of serious acute exacerbations due to fluid overload. Patients should be observed closely during and after administration.
- Elosulfase alfa, laronidase, and olipudase alfa each have a boxed warning for anaphylactic reactions during infusions. Pre-treatment with antihistamines, antipyretics, and/or corticosteroids is recommended, but not required. [25]

Dosing

- The safety and efficacy of doses higher doses than listed in *Table 2* have not been established. Many of the FDA-approved label for injectable ERTs recommends rounding up the dose to the vial size for calculation of the number of vials needed for a given dose. [2 18 30 42 66 68] However, all of the FDA-approved labels for injectable ERTs recommend to "discard any unused product," which would mean to NOT administer the entire rounded vial. [2 7 18 30 42 55 59 63 66 68]

Appendix 1: Non- CNS clinical symptoms of ASMD[27]	
Gastrointestinal symptoms	Hepatosplenomegaly with splenomegaly preceding it, diarrhea, abnormal liver function tests, portal hypertension and liver fibrosis.
Pulmonary symptoms	Interstitial lung disease on imaging, radiographic findings very abnormal with no apparent symptoms, and declining pulmonary function tests.
Cardiac symptoms	Cardiac valve disease, dyslipidemia, and early onset coronary artery disease.
Musculoskeletal symptoms	Bone and joint pain, reduced bone density and pathologic fractures, delayed bone maturation, and growth restriction in childhood.
Hematologic symptoms	Thrombocytopenia with bleeding tendencies.

Cross References
Gaucher Disease Treatments, Medication Policy Manual, Policy No. dru649
Fabry Disease Treatments, Medication Policy Manual, Policy No. dru575
Site of Care Review, Medication Policy Manual, Policy No. dru408
Strensiq, asfotase alfa, Medication Policy Manual, Policy No. dru639

Codes	Number	Description
HCPCS	J0221	Injection, alglucosidase alfa (Lumizyme), 10 mg
HCPCS	J1458	Injection, galsulfase (Naglazyme), 1 mg
HCPCS	J1743	Injection, idursulfase (Elaprase), 1 mg
HCPCS	J1931	Injection, laronidase (Aldurazyme), 0.1 mg
HCPCS	J1322	Injection, elosulfase alfa (Vimizim), 1 mg
HCPCS	J2840	Injection, sebelipase alfa (Kanuma), 1 mg
HCPCS	J3397	Injection, vestronidase alfa-vjbk (Mepsevii), 1 mg
HCPCS	J0219	Injection, avalglucosidase alfa-ngpt (Nexviazyme), 4 mg
HCPCS	J2998	Injection, plasminogen, human-tvmh (Ryplazim), 1 mg
HCPCS	J0127	Injection, velmanase alfa-tycv (Lamzede), 1 mg
HCPCS	J0218	Injection, olipudase alfa-rpcp (Xenpozyme), 1 mg
HCPCS	J1203	Injection, cipaglucosidase alfa-atga (Pombiliti), 5 mg
HCPCS	J1202	Oral, miglustat (Opfolda), 65 mg

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Revision History

Revision Date	Revision Summary
6/20/2024	• Updated Opfolda (miglustat) to include medical OR pharmacy benefit (previously only pharmacy benefit). • Updated criteria for Sucraid (sucrasidase) to clarify biopsy levels indicative of CSID.
03/21/2024	Added coverage criteria for Pombiliti (cipaglucosidase alfa) with Opfolda (miglustat).
9/14/2023	Removed "Clarified wording on Lumizyme vs. Nexviazyme (switch for partial response) based on provider feedback" from revision summary. Change was not made in during annual review.
6/15/2023	• Added coverage criteria for Lamzede (velmanase alfa-tycv). • Clarified wording on Lumizyme vs. Nexviazyme (switch for partial response) based on provider feedback.
12/9/2022	Added coverage criteria for Xenpozyme (olipudase alfa-rpcp).
6/17/2022	• Added generic carglumic acid to the policy. • Added criteria for confirmation of diagnosis for all ERTs, with biochemical, genetic, and/or enzymatic testing. • Added step therapy with generics (carglumic acid, nitisinone) prior to coverage of brands (Carbaglu, Orfadin, Nityr). • Updated Quantity limits (QL): - Updated QL for Kanuma (sebelipase alfa). - Clarified QL for oral ERTs, including acute versus chronic use of carglumic acid. • Clarified COT and reauthorization criteria to include review for use of the lowest effective dose.
11/14/2021	Added Nexviazyme (avalglucosidase alfa) to Site of Care.
10/15/2021	Added coverage criteria for Ryplazim (plasminogen, human-tvmb) and Nexviazyme (avalglucosidase alfa).
7/16/2021	• Clarified that documentation of current weight is required for re-authorization. • Added quantity limits for the use of Carbaglu (carglumic acid) in patients with hyperammonemia due to propionic acidemia (PA) and methylmalonic acidemia (MMA), two newly FDA approved indications. • Removed mentions of Adagen (pegademase bovine) in main criteria, but left in policy backend as it still in appears in prescribing information for Revcovi (elapegademase-lvlr).
7/22/2020	• Added continuation of therapy (COT) criteria.

Revision Date	Revision Summary
	• Removed Myozyme (alglucosidase alfa) and Adagen (pegademase bovine) from the policy. Both products have been discontinued. • Removed Strensiq (asfotase) from policy and created a new policy: dru639 Strensiq, asfotase alfa. • Added new criteria stating that each product must be prescribed by or in conjunction with a specialist for its given disease state.
7/24/2019	• Removed Fabrazyme (agalsidase beta) from policy and added it to dru575 Fabry Disease. • No change to intent of other coverage criteria. Clarification of policy language.
1/31/2019	• Added Revcovi (elapegademase-lvlr) to policy. • Clarified documentation requirements (no change to intent).
11/16/2018	No changes to criteria with this annual update.
3/19/2018	Added Mepsevii (vestronidase alfa) to policy.
1/19/2018	Added Nityr, a new formulation of nitisinone, to policy.
11/11/2016	Removed site of care language from the individual drug policy; however, requirements still apply. Reference to Site of Care Review, dru408 is provided as part of criterion IB.
6/10/2016	Added Kanuma (sebelipase alfa) to policy.
2/12/2016	Added Fabrazyme and Strensiq to policy.
11/13/2015	New policy.

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Medication Policy Manual | **Policy No:** dru440

Topic: Yondelis, trabectedin | **Date of Origin:** January 8, 2016

Committee Approval Date: September 19, 2024 | **Next Review Date:** 2025

Effective Date: December 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Yondelis (trabectedin) is a cytotoxic chemotherapy medication used for the treatment of certain types of soft tissue sarcoma. Yondelis (trabectedin) is given intravenously as a 24-hour infusion through a central line.

Policy/Criteria

Most contracts require pre-authorization approval of Yondelis (trabectedin) prior to coverage.

I. Continuation of therapy (COT): Yondelis (trabectedin) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note: *Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Yondelis (trabectedin) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criterion A, B, or C below is met.

A. A diagnosis of **liposarcoma** (LPS) when criteria 1 and 2 below are met:

1. The LPS is unresectable or metastatic.

AND

2. At least one prior anthracycline-based chemotherapy regimen for LPS has been ineffective (see *Appendix 1*).

OR

B. A diagnosis of **leiomyosarcoma** (LMS) when criteria 1 and 2 below are met:

1. The LMS is unresectable or metastatic.

AND

2. At least one prior anthracycline-based chemotherapy regimen for LMS has been ineffective (see *Appendix 1*).

OR

C. A diagnosis of **translocation-related sarcoma** (TRS) including, but not limited to, synovial sarcoma when criteria 1 and 2 below are met:

1. The TRS is unresectable or metastatic.

AND

2. At least one prior chemotherapy regimen for TRS has been ineffective.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Yondelis (trabectedin) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Yondelis (trabectedin) may be authorized for up to one 24-hour infusion every 21 days, until disease progression.

C. Authorization **may** be reviewed at least every six months. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

IV. Yondelis (trabectedin) is considered not medically necessary when used for the treatment of ovarian cancer.

V. Yondelis (trabectedin) is considered investigational when used for all other conditions, including, but not limited to, soft tissue sarcomas other than listed in Sections I to IV and uterine cancers other than listed in sections I to IV.

Position Statement

Summary

- Yondelis (trabectedin) is a cytotoxic chemotherapy medication used in the treatment of unresectable or metastatic liposarcoma (LPS) or leiomyosarcoma (LMS), or translocation related sarcoma (TRS) after disease progresses on prior cytotoxic chemotherapy.
- The intent of this policy is to cover Yondelis (trabectedin) for the indications, regimen, and dose for which it has been studied, as detailed in the coverage criteria.
- It has not yet been determined if Yondelis (trabectedin) provides clinically meaningful benefit in any of the conditions in which it has been approved. Although Yondelis (trabectedin) demonstrated a progression-free survival (PFS) advantage over standard dose dacarbazine for LPS and LMS, there was no difference in overall survival between groups. Improvement in PFS, a surrogate endpoint, has not been shown to correlate with improvement in any clinically relevant outcome (e.g., symptom control or quality of life).
- *For LPS and LMS*: Standard front-line therapy for unresectable or metastatic soft tissue sarcoma (STS), including LPS and LMS, is anthracycline-based (e.g., doxorubicin) chemotherapy, given either as a single agent or in combination with other cytotoxic agents, because it has been shown to improve survival relative to non-anthracycline-based regimens.
- *For TRS*: Yondelis (trabectedin) has also shown promise in translocation-related sarcomas, including synovial sarcoma. TRSs are rare forms of STS that typically affect younger populations, and for which there are very few treatment options. Patients with advanced disease whose disease has progressed on standard chemotherapy are potential candidates for Yondelis (trabectedin).
- All subjects in the Yondelis (trabectedin) clinical study had progression of disease on prior anthracycline-based chemotherapy. There is no evidence for Yondelis (trabectedin) when given after non-anthracycline-based regimens.
- Yondelis (trabectedin) is a palliative therapy, meaning it is not given with curative intent. National treatment guidelines list Yondelis (trabectedin) among several other therapy options for the palliative treatment of metastatic STS. No one chemotherapy has been shown to be superior to another in this setting.
- Yondelis (trabectedin) is administered as a 24-hour continuous infusion via a central line once every 21 days until progression of disease.
- Yondelis (trabectedin) was evaluated in metastatic ovarian cancer as an add-on to liposomal doxorubicin; however, no difference in OS was demonstrated in the trial. Additionally, there is greater toxicity when these two agents are used together.
- Yondelis (trabectedin) has been evaluated in small numbers of patients with other subtypes of STS; however, data is of extremely low-quality, so the benefit is unknown.
- There are no clinical trials that Yondelis (trabectedin) provides any benefit for patients with uterine cancers other than for leiomyosarcomas and liposarcomas; evidence is limited to scant case reports.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy [1 2]

Liposarcoma and leiomyosarcoma

- The efficacy of Yondelis (trabectedin) is based on a single, published, phase 3 trial in patients with metastatic or recurrent liposarcoma or leiomyosarcoma. These are two of the most common forms of soft tissue sarcoma (STS).
    - All patients in the Yondelis (trabectedin) clinical trial had prior cytotoxic chemotherapy, with the majority having received anthracycline-based regimens, the current front-line standard of care.
    - The study evaluated Yondelis (trabectedin) as a monotherapy in a dose of 1.5 mg/m^2 intravenously as a 24-hour infusion given every 21 days until disease progression. Subjects in the comparator arm received a standard dose of dacarbazine as monotherapy.
    - There was a 2.7-month advantage in progression-free survival (PFS) with Yondelis (trabectedin) versus dacarbazine; however, there was no difference in median overall survival (OS).
    - It is not known if improved PFS correlates with improvements in other clinically relevant outcomes such as symptom control or quality of life.
    - The median duration of response in the Yondelis (trabectedin) and dacarbazine treatment arms was 6.5 months and 4.2 months, respectively. This difference was not statistically significant.
    - There is currently no evidence that Yondelis (trabectedin) is superior to dacarbazine or any other therapy used for the salvage treatment of liposarcoma or leiomyosarcoma with regard to any clinically relevant endpoint.

- Subsequently, Yondelis (trabectedin) was studied as first-line systemic therapy in combination with doxorubicin for chemotherapy-naïve patients with metastatic or unresectable leiomyosarcoma in an open-label phase 3 trial (n=150).[3]
    * The trial compared doxorubicin for up to 6 cycles versus doxorubicin/ Yondelis (trabectedin) for up to 6 cycles induction followed by Yondelis (trabectedin) as maintenance for a maximum of 12 months.
    * The trial enrolled patients with both uterine leiomyosarcoma (n=67) and soft tissue leiomyosarcoma (n=83).
    * Despite a 6-month advantage in PFS with combination Yondelis (trabectedin)/doxorubicin versus doxorubicin alone, overall survival (OS) data was not yet available. It is not known if Yondelis (trabectedin) improved PFS correlates with improvements in overall survival or other clinically relevant outcomes such as symptom control or quality of life.
    * Patients in the combination arm had a higher incidence of grade 3-4 adverse events compared to doxorubicin alone (96% versus 52%, respectively).
    * Several study concerns were identified including open-label design, baseline imbalances favoring the combination therapy arm, and limited generalizability to a healthy population.

<u>Translocation-related sarcomas (TRSs)</u>

- Yondelis (trabectedin) is also being evaluated in advanced translocation-related sarcomas (TRSs), including advanced synovial sarcomas. These rare forms of STS affect younger populations and have few effective treatment options.
    * A pooled analysis of small trials that included patients with different histological subtypes of TRS reported that Yondelis (trabectedin) had anti-tumor effects and prolonged disease control in patients with advanced disease who had a median of one prior therapy regimen. [4]
    * A second study evaluated Yondelis (trabectedin) in patients with metastatic synovial sarcoma who had been treated with prior chemotherapy. A tumor control rate (partial response or stable disease) of 50% was reported. [5]

Guidelines

- The National Comprehensive Cancer Network (NCCN) STS guideline lists Yondelis (trabectedin) as a therapy option as a palliative therapy for liposarcoma (LPS) and leiomyosarcoma (LMS). It is also listed as a therapy option for other subtypes of STS with non-specific histologies as well as for use in the neoadjuvant/adjuvant setting for myxoid liposarcoma. [6]

Not Medically Necessary Uses

- A phase 3 study evaluating Yondelis (trabectedin) plus pegylated liposomal doxorubicin (PLD) versus PLD alone demonstrated improved tumor response rates and progression-free survival (PFS) in the combination arm; however, there was no statistical difference in overall survival based on the mature data set. [7 8]

Investigational Uses

- The safety and effectiveness of Yondelis (trabectedin) in soft tissue sarcomas (STS) other than LPS or LMS have not been adequately assessed. Available studies are in early phases and contain mixed subtypes of STSs with small numbers of any given subtype. [9]
- Yondelis (trabectedin) had no activity in patients with metastatic pancreatic cancer or triple-negative, HER2-overexpressing metastatic breast cancer based on small, preliminary studies. [10 11]
- The safety and effectiveness of Yondelis (trabectedin) in uterine cancer is limited to patients with leiomyosarcoma and liposarcoma histologies; safety and efficacy for use in other uterine cancer histologies have not been adequately assessed. There is no clinical trial evidence for use of Yondelis (trabectedin) in other histologies; data is limited to three case reports in recurrent/ metastatic adenosarcoma. [12]

Safety and Administration [1 2]

- Serious adverse events (AEs) reported with Yondelis (trabectedin) include severe neutropenia, rhabdomyolysis, hepatotoxicity, and cardiomyopathy.
- Yondelis (trabectedin) has only been directly compared with single-agent dacarbazine.
- The incidence of nearly all AEs was numerically higher for Yondelis (trabectedin) than for dacarbazine. Discontinuations due to AEs occurred in 12.6% and 7.7% in the Yondelis (trabectedin) and dacarbazine treatment arms, respectively.
- Yondelis (trabectedin) is administered via a 24-hour continuous infusion. It must be administered via a central line because extravasation can cause tissue necrosis requiring tissue debridement.
- Premedication with dexamethasone is required prior to administration of Yondelis (trabectedin) to prevent or minimize infusion reactions.

Appendix 1: Anthracycline medications
daunorubicin (generics, Cerubidine) doxorubicin (generics, Adriamycin) doxorubicin, liposomal (Doxil, Lipodox) epirubicin (generics, Ellence)

Cross References
Votrient, pazopanib, Medication Policy Manual, Policy No. dru199

Codes	**Number**	**Description**
HCPCS	J9352	Injection, Yondelis (trabectedin) 0.1 mg

References

1. Yondelis (trabectedin) [package insert]. Horsham, PA: Janssen Products LP; June 2020.
2. Demetri GD, von Mehren M, Jones RL, et al. Efficacy and Safety of Trabectedin or Dacarbazine for Metastatic Liposarcoma or Leiomyosarcoma After Failure of Conventional Chemotherapy: Results of a Phase III Randomized Multicenter Clinical Trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2015. PMID: 26371143
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Revision History

Revision Date	Revision Summary
9/19/2024	No criteria changes with this annual review.
9/14/2023	No criteria changes with this annual review.
9/23/2022	No coverage criteria changes with this annual update.
10/15/2021	- Continuation of therapy (COT) language updated for standardization. - No coverage criteria changes with this annual update.
10/28/2020	- Continuation of therapy (COT) language added. - Updated investigational indications to explicitly call out uterine cancers other than what is covered in criteria but no change to intent. - No coverage criteria changes with this annual update.
10/23/2019	No coverage criteria changes with this annual update.
10/19/2018	- Updated policy with standard language, including clarifying the Authorization Period to state 'until disease progression' (no change to policy intent) - Added coverage for TRS (few other options)
1/13/2017	- No coverage criteria changes. - Updated references for package labeling and NCCN guideline, and added documentation for two additional populations where trabectedin was not found to have activity.
1/8/2016	New policy.

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Medication Policy Manual

Policy No: dru443

Topic: Onivyde, irinotecan liposome injection

Date of Origin: January 8, 2016

Committee Approval Date: March 6, 2025

Next Review Date: 2026

Effective Date: May 1, 2025

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Onivyde (liposomal irinotecan) is an intravenous formulation of generic irinotecan HCL. It is a nanoliposomal encapsulation of irinotecan HCL molecules. Liposomal irinotecan (Onivyde) is indicated for patients with metastatic pancreatic cancer who have progressed on prior gemcitabine-based chemotherapy. It is given in combination with fluorouracil and leucovorin.

PLEASE NOTE: This policy and the criteria below do not apply to non-liposomal forms of intravenous irinotecan (generic, Camptosar). Non-liposomal generic irinotecan and brand Camptosar IV solution do not require pre-authorization.

Policy/Criteria

Most contracts require pre-authorization approval of Onivyde (liposomal irinotecan) prior to coverage.

I. Continuation of therapy (COT): Onivyde (liposomal irinotecan) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Onivyde (liposomal irinotecan) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A, B, and C below are met.

A. A diagnosis of **metastatic pancreatic cancer**.

AND

B. There has been disease progression following gemcitabine-based chemotherapy.

AND

C. Onivyde (liposomal irinotecan) will be given in combination with fluorouracil and leucovorin.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Onivyde (liposomal irinotecan) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Onivyde (liposomal irinotecan) may be authorized in doses up to 70 mg/m^2 every two weeks until disease progression.

C. Authorization **may** be reviewed at least every six months. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

IV. Onivyde (liposomal irinotecan) is considered not medically necessary when used in the following settings:

A. As monotherapy for metastatic pancreatic cancer.

B. As front-line therapy for metastatic pancreatic cancer (e.g., as part of the NALIRIFOX chemotherapy regimen).

V. Onivyde (liposomal irinotecan) is considered investigational when used for all other conditions, including but not limited to:

A. Colorectal cancer.

B. Gastric cancer.

C. High grade glioma.

D. Lung cancer.

E. Osteosarcoma.

F. Soft tissue sarcoma.

Position Statement

Summary

- Onivyde (liposomal irinotecan) is an intravenously administered medication for the treatment of metastatic pancreatic cancer.
- For progressive metastatic pancreatic cancer:
  * Onivyde (liposomal irinotecan) has only been studied in the post-gemcitabine setting (i.e., as a second-line therapy following progression of disease on gemcitabine-based chemotherapy).
  * Although the pivotal trial for the approval of Onivyde (liposomal irinotecan) included a monotherapy arm, use of Onivyde (liposomal irinotecan) without fluorouracil and leucovorin did not demonstrate improvements in overall survival (OS) compared to the combination, therefore Onivyde (liposomal irinotecan) monotherapy is considered not medically necessary.
- The FDA labeling states that Onivyde (liposomal irinotecan) is not indicated as a single agent for the treatment of patients with metastatic pancreatic cancer.
- Front-line metastatic pancreatic cancer: Although Onivyde (liposomal irinotecan) was evaluated as part of a front-line regimen (NALIRIFOX) for metastatic pancreatic cancer it is not known whether it is superior to more cost-effective, standard-of-care front-line regimens such as FOLFIRINOX.
- The recommended dose of Onivyde (liposomal irinotecan) is 70 mg/m^2 every two weeks until disease progression or unacceptable toxicity. The safety and effectiveness of higher doses or more frequent dosing have not been established. [1]
- There is currently no published data that evaluates the safety and efficacy of Onivyde (liposomal irinotecan) in any other cancer setting.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy

Progressive metastatic pancreatic cancer:

- The effectiveness of Onivyde (liposomal irinotecan) was evaluated in a single, open-label, randomized clinical trial in patients with metastatic pancreatic cancer with documented disease progression, after gemcitabine or gemcitabine-based therapy. [2] Patients with locally advanced disease were not included in the study population.
    * The primary endpoint of the pivotal trial was overall survival (OS). Combination treatment with Onivyde (liposomal irinotecan) and fluorouracil and leucovorin resulted in a two-month improvement in median OS compared to fluorouracil and leucovorin alone.
    * In the Onivyde (liposomal irinotecan) monotherapy arm, there was no statistically significant difference is median OS compared to fluorouracil and leucovorin alone.
- There is currently no established standard of care for the treatment of metastatic pancreatic cancer in the second-line setting; participation in a clinical trial is the preferred when available. The National Comprehensive Cancer Network (NCCN) Pancreatic Adenocarcinoma guideline recommends Onivyde (liposomal irinotecan), gemcitabine-based chemotherapy or fluoropyrimidine-based chemotherapy, depending on the agents used in the first-line setting. Onivyde (liposomal irinotecan) is considered a category 1 recommendation for patients previously treated with gemcitabine-based therapy. [3]

Front-line setting, metastatic pancreatic cancer:

- Subsequently, Onivyde (liposomal irinotecan) was evaluated in an open-label, randomized controlled trial (NAPOLI 3) where it was shown to incrementally improve OS relative to gemcitabine plus nab-paclitaxel when given as part of the NALIRIFOX regimen [Onivyde (liposomal irinotecan), oxaliplatin, leucovorin, and fluorouracil]. However, it is unknown how NALIRIFOX compares with other front-line, standard-of-care regimens for metastatic pancreatic cancer, such as FOLFIRINOX, which provides a better value. [4] Furthermore, a meta-analysis comparing NALIRIFOX and FOLFIRINOX in the front-line treatment of metastatic pancreatic cancer found these two regimens to be similar with regard to OS benefit suggesting there is no efficacy advantage in substituting Onivyde (irinotecan liposomal) for standard irinotecan in this treatment setting. [5]
- The NCCN pancreatic cancer guideline lists gemcitabine plus nab-paclitaxel, FOLFIRINOX, and NALIRIFOX among first-line, preferred recommendations for advanced pancreatic cancer. The guideline notes that the Onivyde (irinotecan liposomal)-based regimen (NALIRIFOX) adds considerable expense over FOLFIRINOX without any apparent advantages in this setting. [3]

Investigational Uses

- Onivyde (liposomal irinotecan) is being studied in a variety of other cancers such as colorectal cancer, gastric cancer, high grade glioma, lung cancer, osteosarcoma, and soft tissue sarcoma. [6]

- Although Onivyde (liposomal irinotecan) is being studied for the treatment of various cancers, there is currently no published evidence supporting its safety or efficacy in these settings.
- A phase 3 study (RESILIENT) comparing Onivyde (liposomal irinotecan) with topotecan in patients with advanced small cell lung cancer that had progressed on or after front-line platinum-based chemotherapy failed to meet its endpoint of improved OS. [7]
- There is interest in using Onivyde (liposomal irinotecan) in metastatic biliary tract cancer (including in intra- and extrahepatic cholangiocarcinoma) based on a small trial (NIFTY study) conducted at five study sites in South Korea. [8]
    * The trial compared the addition of Onivyde (liposomal irinotecan) to fluorouracil plus leucovorin and compared it with fluorouracil/leucovorin alone.
    * Authors reported a 3-month OS advantage in the Onivyde (liposomal irinotecan) treatment arm. However, there are many uncertainties in the data including the statistical methods, and the choice of comparator.
    * FOLFOX (oxaliplatin/fluorouracil/leucovorin) is the standard of care in the U.S., so the clinical relevance of the results is unknown.
    * The NCCN lists the use of Onivyde (liposomal irinotecan) in biliary tract cancer as a category 2B recommendation.

Cross References		
Abraxane, nab-paclitaxel, (a.k.a. albumin-bound paclitaxel, paclitaxel albumin-stabilized nanoparticle formulation, ABI-007) Medication Policy Manual, Policy No. 310		
Codes	**Number**	**Description**
HCPCS	C9474	Injection, irinotecan liposome (Onivyde), 1 mg
HCPCS	J9205	Injection, irinotecan liposome (Onivyde), 1 mg

References

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Revision History

Revision Date	Revision Summary
3/6/2025	No changes to coverage criteria with this annual review.
9/19/2024	• No changes to coverage criteria with this ad hoc review [the use of Onivyde (irinotecan liposomal) as part of the NALIRIFOX regimen is already considered not medically necessary based on a prior annual review].
12/7/2023	• Changed front-line use of Onivyde (liposomal irinotecan) from 'Investigational' to 'Not Medically Necessary' based on new evidence in the front-line metastatic pancreatic cancer setting. Although Onivyde (liposomal irinotecan) appears to have efficacy as part of a front-line therapy regimen in this setting other more established front-line regimens such as FOLFIRINOX provide a better value.
12/9/2022	• Updated standard language in policy. • No changes to coverage criteria with this annual update.
1/20/2021	Updated continuation of therapy (COT) language. No changes to coverage criteria.
1/22/2020	Added continuation of therapy (COT) criteria (no change to intent of coverage criteria).
1/31/2018	No criteria changes with this annual update.
11/10/2017	No criteria changes with this annual review.
1/13/2017	No criteria changes with this annual review.
1/8/2016	New policy

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Medication Policy Manual

Policy No: dru444

Topic: Drugs for chronic inflammatory diseases

Date of Origin: January 8, 2016

- adalimumab (Humira; biosimilars: Abrilada, Amjevita, Cyltezo, Hadlima, Hulio, Hyrimoz, Idacio, Simlandi, Yuflyma, Yusimry; unbranded: adalimumab-adaz, adalimumab-adbm, adalimumab-ryvk)
- Adbry, tralokinumab-ldrm
- Bimzelx, bimekizumab-bkzx
- Cibinqo, abrocitinib
- Cimzia, certolizumab pegol
- Cosentyx, secukinumab
- Entyvio, vedolizumab
- etanercept (Enbrel; biosimilars Erelzi, Eticovo)
- golimumab (Simponi, Simponi Aria)
- Ilumya, tildrakizumab-asmn
- Kevzara, sarilumab
- Litfulo, ritlecitinib
- Olumiant, baricitinib
- Omvoh, mirikizumab-mrkz
- Orencia, abatacept
- Otezla, apremilast
- Siliq, brodalumab
- Skyrizi, risankizumab-rzaa
- Sotyktu, deucravacitinib
- Spevigo, spesolimab-sbzo
- Stelara, ustekinumab
- Taltz, ixekizumab
- tocilizumab (Actemra; biosimilars Tofidence, Tyenne)
- tofacitinib (Xeljanz, Xeljanz XR)
- upadacitinib (Rinvoq, Rinvoq LQ)
- Tremfya, guselkumab
- Velsipity, etrasimod

Committee Approval Date: June 20, 2024

Next Review Date: 2025

Effective Date: October 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Administration of Contract

Coverage for cosmetic purposes, including removal, inhibition, or stimulation of hair growth, is defined by benefit contract language.

Description

Medications included in this policy are used to treat a group of diseases that may be caused or worsened by an overactive immune system. Administration may be a subcutaneous injection (SC), intravenous injection (IV), or administered by mouth.

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	IL-1	- Kineret (anakinra) [a] - Ilaris (canakinumab) [a]	
JAK Inhibitors	JAK1/2/3	- Cibinqo (abrocitinib) - Litfulo (ritlecitinib) - Olumiant (baricitinib) - Tofacitinib (Xeljanz, Xeljanz XR) - Rinvoq (upadacitinib)	
	TYK2	- Sotyktu (deucravacitinib)	
PDE-4 Inhibitors		- Otezla (apremilast)	
S1P receptor modulator		- Velsipity (etrasimod)	
Conventional synthetic DMARDs (csDMARD) (also referred to as conventional immunomodulators)		- Azathioprine (generic, Imuran) - 6-mercaptopurine (generic, 6-MP) - Methotrexate (generic, MTX) - Hydroxychloroquine (HCQ; generic, Plaquenil) - Leflunomide (generic, Arava) - Mycophenolate (MMF; generic, CellCept, Myfortic)	- Cyclosporine (CSA; Gengraf, Neoral, Sandimmune) - Tacrolimus (generic, Prograf) - 5 ASAs [sulfasalazine (generic, SSZ), mesalamine, balsalazide] - Acitretin (generic, Accutane)

[a] See "Cross References" for associated policy for this medication

Policy/Criteria

Most contracts require prior authorization approval of medications used to treat chronic inflammatory diseases prior to coverage.

I. Continuation of therapy (COT): Medications in this policy may be considered medically necessary for COT when criterion A, B, or C, **AND** D **AND** E below is met.

A. For diagnoses NOT listed in the coverage criteria below, full policy criteria must be met for coverage.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. With exception of Olumiant (baricitinib) use for coronavirus-19 (COVID-19), the medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

AND

D. **For Provider-administered drugs only (as applicable):** Site of care administration requirements are met [refer to Medication Policy Manual, Site of Care Review, dru408].

AND

E. **"Administration of Contract" is met.**

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Medications in this policy may be considered medically necessary when the criteria below are met.

A. Acute Graft Versus Host Disease (aGVHD), Prophylaxis
Orencia (abatacept) IV may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria 1, 2, and 3 below are met. **1.** Abatacept will be used for **prophylaxis of acute graft versus host disease (aGVHD)**. **AND** **2.** Patient will undergo a hematopoietic cell transplant (HCT) from an unrelated donor (either 8/8 HLA matched or 7/8 HLA mismatch). **AND** **3.** Abatacept will be used in combination with methotrexate and a calcineurin inhibitor (cyclosporine or tacrolimus).

B. Alopecia areata (AA)

Note: medications for cosmetic purposes, including, but not limited to the stimulation of hair growth is dictated by benefit contract language.

1. **Diagnostic Criteria:** The diagnosis of alopecia areata (AA) has been established by or in conjunction with a specialist in dermatology.
2. **Severity Criteria:** Criteria a, b, and c below are met.
   a. Severe AA as indicated by a severity of alopecia tool (SALT) score of ≥ 50 or ≥ 50% scalp hair loss.

   AND

   b. No evidence of terminal hair regrowth within 6 months.

   AND

   c. Both the following have been ineffective or not tolerated, unless all are contraindicated:
      i. At least 6 months of a conventional oral immunosuppressant (methotrexate, cyclosporine, or azathioprine)

      AND

      ii. Either A or B below:

      A. At least 6 weeks of topical or oral corticosteroid therapy.

      OR

      B. At least 6 months of topically immunotherapy (diphenylcyclopropenone [DPCP] or squaric acid dibutyl ester [SADBE]).

Product Group	Products	Criteria Requirements
Level 1	- Litfulo (ritlecitinib) - Olumiant (baricitinib)	**1.** Diagnostic Criteria **2.** Severity Criteria

C. Ankylosing Spondylitis (AS) – Self-administered Products		
1. <u>Diagnostic Criteria</u>: A diagnosis of **axial SpA**, including **ankylosing spondylitis** (AS), when established by or in consultation with a specialist in rheumatology.		
Product Group	**Products**	**Criteria Requirements**
Level 1	- Cosentyx (secukinumab) - Enbrel (etanercept) - Hadlima (adalimumab-bwwd) - Humira (adalimumab) - Simlandi (adalimumab-ryvk)	**1.** Diagnostic Criteria
Level 2	- Rinvoq (upadacitinib) - Xeljanz/Xeljanz XR (tofacitinib)	**1.** Diagnostic Criteria **2.** There is clinical documentation that treatment with **at least ONE Level 1** TNF-inhibitor was not effective after at least a 12-week treatment course unless all were not tolerated or are contraindicated.
Level 3	- Cimzia (certolizumab pegol) syringes - Simponi (golimumab) SC - Taltz (ixekizumab)	**1.** Diagnostic Criteria **2.** There is clinical documentation that treatment with **at least TWO Level 1 or Level 2** therapies was not effective after at least a 12-week treatment course unless all were not tolerated or are contraindicated.
Non-Preferred Adalimumab Products	- Adalimumab biosimilars (Abrilada, Amjevita, Cyltezo, Hulio, Hyrimoz, Idacio, Yuflyma, Yusimry)	**1.** Diagnostic Criteria **2.** There is a documented intolerance or contraindication to **Humira (adalimumab), Hadlima (adalimumab-bwwd), and Simlandi (adalimumab-ryvk).**
Non-Preferred Etanercept Products	- Etanercept biosimilars (Erelzi, Eticovo)	**1.** Diagnostic Criteria **2.** There is a documented intolerance or contraindication to **Enbrel (etanercept)**.

D. Ankylosing Spondylitis (AS) – Provider-administered Products		
1. **Site of Care Requirements:** For provider-administered therapies, site of care administration requirements are met [refer to Medication Policy Manual, Site of Care Review, dru408]. **2.** **Diagnostic Criteria:** A diagnosis of **axial SpA**, including **ankylosing spondylitis** (AS), when established by or in consultation with a specialist in rheumatology.		
Product Group	**Products**	**Criteria Requirements**
Level 1	- Cosentyx (secukinumab) IV - Simponi Aria (golimumab) IV	**1.** Site of Care Requirements **2.** Diagnostic Criteria
	- Avsola, Inflectra (infliximab)	Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620
Level 2	- Cimzia (certolizumab pegol) vials	**1.** Site of Care Requirements **2.** Diagnostic Criteria **3.** There is clinical documentation that treatment with **at least TWO Level 1** therapies was not effective after at least a 12-week treatment course unless all were not tolerated or are contraindicated.
Non-Preferred Infliximab Products	- Infliximab biosimilars (Renflexis, Ixifi) - Remicade (infliximab) - Unbranded Janssen infliximab product	Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620

E. Antibody Mediated Rejection (AMR) of Transplant (Solid Organ)		
Tocilizumab IV may be considered medically necessary when criteria 1 and 2 below are met. **1.** **Diagnostic Criteria:** Criterion a or b below are met. **a.** **Prevention of antibody (Ab)-mediated rejection:** Prior to solid organ transplant and in the peri-operative period, for patients at high risk for Ab-mediated rejection, including highly sensitized patients, and those receiving an ABO-incompatible organ. **OR** **b.** **Treatment of antibody-mediated rejection** (a.k.a. vascular rejection, humoral rejection): Following solid organ transplant and confirmed by either biopsy or presence of panel reactive antibodies (PRAs). **AND** **2.** **Severity Criteria:** Treatment with immunoglobulin (IVIG), plasma exchange/pheresis (PLEX), and rituximab has been ineffective or is contraindicated.		
Product Group	**Products**	**Criteria Requirements**
Level 1	- Actemra (tocilizumab) IV - Tyenne (tocilizumab-aazg) IV	**1.** Diagnostic Criteria **2.** Severity Criteria
Non-Preferred Tocilizumab Products	- Tocilizumab biosimilar (Tofidence) IV	**1.** Diagnostic Criteria **2.** Severity Criteria **3.** There is a documented intolerance or contraindication to **all Level 1** therapies.

F. Atopic Dermatitis (AD) – Self-administered Products

1. **Diagnostic Criteria:** The medication is being prescribed by or in conjunction with a specialist in dermatology, allergy, or pulmonology.
2. **Severity Criteria:** All the following criteria a, b, and c below are met.
   - **a.** The patient is age 12 or older for Rinvoq (upadacitinib), Cibinqo (abrocitinib), or Adbry (tralokinumab-ldrm).

   AND

   - **b.** The patient has a diagnosis of moderate to severe atopic dermatitis.

   AND

   - **c.** Both the following (i and ii) have been ineffective or not tolerated, unless all are contraindicated:
     - **i.** A medium to very high-potency corticosteroid (see *Appendix 1*), for at least 14 days.

     AND

     - **ii.** Topical tacrolimus, for at least 28 days, unless one of the following apply (criterion a or b below):
       - **a.** Atopic dermatitis affects a body surface area (BSA) greater than or equal to 10% or involvement of a hairy area of the body (such as the scalp) such that use of topical tacrolimus is not feasible.

       OR

       - **b.** Systemic immunosuppressants (such as oral cyclosporine, methotrexate, azathioprine, mycophenolate mofetil, or a biologic) for at least two months have been ineffective, not tolerated, or all are contraindicated.

PLEASE NOTE: Ineffectiveness for topical agents is defined as failure to achieve and maintain remission or a low disease activity state despite treatment with a daily regimen, applied for ≥ 28 days or for the maximum duration recommended by the product prescribing information (e.g., 14 days for high or very-high potency topical corticosteroids).

Product Group	Products	Criteria Requirements
Level 1	- Adbry (tralokinumab-ldrm) - Cibinqo (abrocitinib) - Rinvoq (upadacitinib)	**1.** Diagnostic Criteria **2.** Severity Criteria
	- Dupixent (dupilumab)	Refer to Medication Policy Manual, Dupixent, dupilumab, dru493

G. Non-Radiographic Axial Spondyloarthritis (Nr-axSpA) – Self-administered Products		
1. <u>Diagnostic Criteria</u>: A diagnosis of **non-radiographic axial spondyloarthritis** (Nr-axSpA) when established by or in consultation with a specialist in rheumatology.		
Product Group	**Products**	**Criteria Requirements**
Level 1	- Cimzia (certolizumab pegol) syringes - Cosentyx (secukinumab)	**1.** Diagnostic Criteria
Level 2	- Rinvoq (upadacitinib)	**1.** Diagnostic criteria **2.** There is clinical documentation that treatment with **at least ONE level 1 TNF** inhibitor was not effective after at least a 12-week treatment course unless all were not tolerated or are contraindicated.
Level 3	- Taltz (ixekizumab)	**1.** Diagnostic Criteria **2.** There is clinical documentation that treatment with **at least TWO Level 1 or Level 2** therapies was not effective after at least a 12-week treatment course unless all were not tolerated or are contraindicated.

H. Non-Radiographic Axial Spondyloarthritis (Nr-axSpA) – Provider-administered Products		
1. **Site of Care Requirements:** For provider-administered therapies, site of care administration requirements are met [refer to Medication Policy Manual, Site of Care Review, dru408]. **2.** **Diagnostic Criteria:** A diagnosis of **non-radiographic axial spondyloarthritis** (Nr-axSpA) established by or in consultation with a specialist in rheumatology.		
Product Group	**Products**	**Criteria Requirements**
Level 1	- Cimzia (certolizumab pegol) vials - Cosentyx (secukinumab) IV	**1.** Site of Care Requirements **2.** Diagnostic Criteria

I. Behçet's Disease (BD)		
1. **<u>Diagnostic Criteria</u>:** The diagnosis of **Behçet's Disease** (BD) has been established by or in conjunction with a specialist in rheumatology, dermatology, or immunology. **2.** **<u>Severity Criteria</u>:** All the following criteria a, b, and c below are met. **a.** There is documentation of mucocutaneous ulcers (including, but not limited to, oral, genital, or cutaneous ulcers). **AND** **b.** Documentation confirming functional impairment due to BD, which may include, but is not limited to, limitation of activities of daily living (ADLs), such as infections, severe pain, or sleep disturbances. **AND** **c.** Treatment with colchicine, azathioprine, cyclosporine, methotrexate, a topical corticosteroid (e.g., triamcinolone dental paste), or other immunomodulator (see *Appendix 3*) for at least four weeks has been ineffective or not tolerated, unless all are contraindicated.		
Product Group	**Products**	**Criteria Requirements**
Level 1	- Otezla (apremilast)	**1.** Diagnostic Criteria **2.** Severity Criteria

J. Chronic Plaque Psoriasis (PsO) – Self-administered Products

1. **Diagnostic Criteria:** A diagnosis of **chronic plaque psoriasis** (PsO) when established by or in consultation with a specialist in dermatology or rheumatology.
2. **Severity Criteria:** At least one of the following criterion a, b, or c below are met.
   - **a.** There is involvement of ≥ 10% of the body surface (BSA) area OR there is significant functional disability due to PsO.

     OR
   - **b.** Treatment with phototherapy (for example, UVB) or photochemotherapy was not effective, not tolerated, or is contraindicated (such as lesions on the face, scalp, hands, feet, nailbeds, or groin area; see *Appendix 2*).

     OR
   - **c.** Treatment with at least one oral/topical conventional medication therapy was not effective after 12 weeks, not tolerated, or all are contraindicated. Conventional medication therapies for the treatment of PsO include: acitretin, anthralin, calcipotriene, calcitriol, coal tar products, cyclosporine, methotrexate, pimecrolimus, tacrolimus, tazarotene, or a topical corticosteroid.

Product Group	Products	Criteria Requirements
Level 1	- Cosentyx (secukinumab) - Enbrel (etanercept) - Hadlima (adalimumab-bwwd) - Humira (adalimumab) - Otezla (apremilast) - Simlandi (adalimumab-ryvk) - Skyrizi (risankizumab) - Stelara (ustekinumab) - Tremfya (guselkumab)	**1.** Diagnostic Criteria **2.** Severity Criteria
Level 2	- Sotyktu (deucravacitinib)	1. Diagnostic Criteria 2. Severity Criteria 3. There is clinical documentation that treatment with **at least ONE Level 1 therapy** was not effective after at least a 12-week treatment course unless all were not tolerated or are contraindicated. 4.
Level 3	- Cimzia (certolizumab pegol) syringes	**1.** Diagnostic Criteria **2.** Severity Criteria **3.** There is clinical documentation that treatment with **at least TWO Level 1 therapies** was not effective after at least a 12-week treatment course unless all were not tolerated or are contraindicated.

J. Chronic Plaque Psoriasis (PsO) – Self-administered Products		
Product Group	**Products**	**Criteria Requirements**
Level 4	- Bimzelx (bimekizumab-bkzx) - Siliq (brodalumab) - Taltz (ixekizumab)	**1.** Diagnostic Criteria **2.** Severity Criteria **3.** There is clinical documentation that treatment with **at least THREE Level 1** therapies was not effective after at least a 12-week treatment course unless all were not tolerated or are contraindicated.
Non-Preferred Adalimumab Products	- Adalimumab biosimilars (Abrilada, Amjevita, Cyltezo, Hulio, Hyrimoz, Idacio, Yuflyma, Yusimry)	**1.** Diagnostic Criteria **2.** Severity Criteria **3.** There is a documented intolerance or contraindication to **Humira (adalimumab), Hadlima (adalimumab-bwwd), and Simlandi (adalimumab-ryvk).**
Non-Preferred Etanercept Products	- Etanercept biosimilars (Erelzi, Eticovo)	**1.** Diagnostic Criteria **2.** Severity Criteria **3.** There is a documented intolerance or contraindication to **Enbrel (etanercept)**.

K. Chronic Plaque Psoriasis (PsO) – Provider-administered Products

1. **Site of Care Requirements:** For provider-administered therapies, site of care administration requirements are met [refer to Medication Policy Manual, Site of Care Review, dru408].
2. **Diagnostic Criteria:** A diagnosis of **chronic plaque psoriasis** (PsO) when established by or in consultation with a specialist in dermatology or rheumatology.
3. **Severity Criteria:** At least one of the following criterion a, b, or c below are met.
   - **a.** There is involvement of ≥ 10% of the body surface (BSA) area OR there is significant functional disability due to PsO.

   OR

   - **b.** Treatment with phototherapy (for example, UVB) or photochemotherapy was not effective, not tolerated, or is contraindicated (such as lesions on the face, scalp, hands, feet, nailbeds, or groin area; see *Appendix 2*).

   OR

   - **c.** Treatment with at least one oral/topical conventional medication therapy was not effective after 12 weeks, not tolerated, or all are contraindicated. Conventional medication therapies for the treatment of PsO include: acitretin, anthralin, calcipotriene, calcitriol, coal tar products, cyclosporine, methotrexate, pimecrolimus, tacrolimus, tazarotene, or a topical corticosteroid.

Product Group	Products	Criteria Requirements
Level 1	- Stelara (ustekinumab)	**1.** Diagnostic Criteria **2.** Severity Criteria
	- Avsola, Inflectra (infliximab)	Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620
Level 2	- Cimzia (certolizumab pegol) vials - Ilumya (tildrakizumab-asmn)	**1.** Site of Care Requirements (*Cimzia vials only*) **2.** Diagnostic Criteria **3.** Severity Criteria **4.** There is clinical documentation that treatment with **at least TWO Level 1** therapies was not effective after at least a 12-week treatment course unless all were not tolerated or are contraindicated.
Non-Preferred Infliximab Products	- Infliximab biosimilars (Renflexis, Ixifi) - Remicade (infliximab) - Unbranded Janssen infliximab product	Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620

L. Crohn's Disease (CD) – Self-administered Products

1. **Diagnostic Criteria:** A diagnosis of **Crohn's disease** (CD) established by or in consultation with a specialist in gastroenterology.
2. **Severity Criteria:** Either criterion a or b below are met.
   - **a.** At least one of the following criterion (i through vi) below are met.
     - **i.** Fistulizing Crohn's disease.
     - **ii.** Previous hospitalization for Crohn's disease.
     - **iii.** Extensive anatomic involvement.
     - **iv.** Deep ulcers.
     - **v.** Prior surgical resection.
     - **vi.** Stricturing and/or penetrating behavior.

   OR

   - **b.** Acute treatment of an exacerbation when at least one of criterion (i, ii, or iii) below is met.
     - **i.** Treatment with an adequate course of corticosteroids (for example, prednisone 40 to 60 mg/day, oral budesonide 9 mg/day, or budesonide rectal for 7 to 14 days) has been ineffective or is contraindicated.

     OR

     - **ii.** The patient has been unable to taper an adequate course of corticosteroids without experiencing worsening of disease.

     OR

     - **iii.** The patient is experiencing breakthrough disease (e.g., active disease flares) while stabilized for at least 8 weeks on a conventional immunomodulator. Conventional immunomodulators for CD include azathioprine, mercaptopurine, methotrexate, balsalazide, mesalamine, cyclosporine, and sulfasalazine.

Product Group	Products	Criteria Requirements
Level 1	- Hadlima (adalimumab-bwwd) - Humira (adalimumab) - Simlandi (adalimumab-ryvk) - Skyrizi (risankizumab-rzaa) - Stelara (ustekinumab)	**1.** Diagnostic Criteria **2.** Severity Criteria
Level 2	- Upadacitinib (Rinvoq)	**1.** Diagnostic Criteria **2.** Severity Criteria **3.** Treatment with adalimumab was not effective after at least a 12-week treatment course unless not tolerated or contraindicated.
Level 3	- Cimzia (certolizumab pegol) syringes - Entyvio (vedolizumab) SC	**1.** Diagnostic Criteria **2.** Severity Criteria **3.** Treatment with **TWO Level 1 or 2 therapies** were not effective after at least 12 weeks of treatment each, unless not tolerated or contraindicated. For members established on Entyvio (vedolizumab) IV therapy, this criterion may be waived.

L. Crohn's Disease (CD) – Self-administered Products		
Product Group	**Products**	**Criteria Requirements**
Non-Preferred Adalimumab Products	- Adalimumab biosimilars (Abrilada, Amjevita, Cyltezo, Hulio, Hyrimoz, Idacio, Yuflyma, Yusimry)	**1.** Diagnostic Criteria **2.** Severity Criteria **3.** There is a documented intolerance or contraindication to **Humira (adalimumab), Hadlima (adalimumab-bwwd), and Simlandi (adalimumab-ryvk).**
Non-Preferred Infliximab Products	- Infliximab products (Zymfentra)	Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620

M. Crohn's Disease (CD) – Provider-administered Products

1. **Site of Care Requirements:** For provider-administered therapies, site of care administration requirements are met [refer to Medication Policy Manual, Site of Care Review, dru408].
2. **Diagnostic Criteria:** A diagnosis of **Crohn's disease** (CD) established by or in consultation with a specialist in gastroenterology.
3. **Severity Criteria:** Either criterion a or b below are met.
   - **a.** At least one of the following criteria (I through vi) below are met.
     - **i.** Fistulizing Crohn's disease.
     - **ii.** Previous hospitalization for Crohn's disease.
     - **iii.** Extensive anatomic involvement.
     - **iv.** Deep ulcers.
     - **v.** Prior surgical resection.
     - **vi.** Stricturing and/or penetrating behavior.

   OR

   - **b.** Acute treatment of an exacerbation when at least one of criterion (i, ii, or iii) below, is met.
     - **i.** Treatment with an adequate course of corticosteroids (for example, prednisone 40 to 60 mg/day, oral budesonide 9 mg/day, or budesonide rectal for 7 to 14 days) has been ineffective or is contraindicated.

     OR

     - **ii.** The patient has been unable to taper an adequate course of corticosteroids without experiencing worsening of disease.

     OR

     - **iii.** The patient is experiencing breakthrough disease (e.g., active disease flares) while stabilized for at least 8 weeks on a conventional immunomodulator. Conventional immunomodulators for CD include azathioprine, mercaptopurine, methotrexate, balsalazide, mesalamine, cyclosporine, and sulfasalazine.

Product Group	Products	Criteria Requirements
Level 1	- Entyvio (vedolizumab) - Skyrizi 21isankizumabb-rzaa) - Stelara (ustekinumab)	**1.** Site of Care Requirements *(Entyvio only)* **2.** Diagnostic Criteria **3.** Severity Criteria
	- Avsola, Inflectra (infliximab)	Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620
Level 2	- Cimzia (certolizumab pegol) vials	**1.** Site of Care Requirements **2.** Diagnostic Criteria **3.** Severity Criteria **4.** Treatment with **at least TWO Level 1** therapies was not effective after at least a 12-week treatment course unless all were not tolerated or are contraindicated.

M. Crohn's Disease (CD) – Provider-administered Products		
Product Group	**Products**	**Criteria Requirements**
Non-Preferred Infliximab Products	- Infliximab biosimilars (Renflexis, Ixifi) - Remicade (infliximab) - Unbranded Janssen infliximab product	Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620

N. Cytokine-release Syndrome (CRS)		
Tocilizumab IV may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criterion 1 below is met. **1. Product will be used for cytokine release syndrome** (CRS)**.**		
Product Group	**Products**	**Criteria Requirements**
Level 1	- Actemra (tocilizumab) IV - Tyenne (tocilizumab-aazg) IV	**1.** Diagnostic Criteria
Non-Preferred Tocilizumab Products	- Tocilizumab biosimilar (Tofidence IV)	**1.** Diagnostic Criteria **2.** There is a documented intolerance or contraindication to **all Level 1** therapies.

O. Enthesitis-related Arthritis (ERA)		
1. <u>Diagnostic Criteria</u>: A diagnosis of enthesitis-related arthritis (ERA) when established by or in consultation with a specialist in rheumatology.		
Product Group	**Products**	**Criteria Requirements**
Level 1	- Cosentyx (secukinumab) - Enbrel (etanercept) - Hadlima (adalimumab-bwwd) - Humira (adalimumab) - Simlandi (adalimumab-ryvk)	**1.** Diagnostic Criteria
Non-Preferred Adalimumab Products	- Adalimumab biosimilars (Abrilada, Amjevita, Cyltezo, Hulio, Hyrimoz, Idacio, Yuflyma, Yusimry)	**1.** Diagnostic Criteria **2.** There is a documented intolerance or contraindication to **Humira (adalimumab), Hadlima (adalimumab-bwwd), and Simlandi (adalimumab-ryvk).**
Non-Preferred Etanercept Products	- Etanercept biosimilars (Erelzi, Eticovo)	**1.** Diagnostic Criteria **2.** There is a documented intolerance or contraindication to **Enbrel (etanercept)**.

P. Generalized Pustular Psoriasis (GPP) – Self-administered Products

Spevigo (spesolimab-sbzo) SC may be considered medically necessary when criteria 1 and 2 below are met.

1. **Diagnostic Criteria:** A diagnosis of **generalized pustular psoriasis (GPP)** when established by or in consultation with a specialist in dermatology.
2. **Severity Criteria: Maintenance treatment for GPP (SC formulation only)** when criteria a, b, and c below are met.
   - **a.** History of at least two moderate-to-severe flares with at least one associated with fever, elevated C-reactive protein level, elevated white blood cell count, asthenia, or myalgia.

   AND

   - **b.** Currently not experiencing a flare.

   AND

   - **c.** Treatment with acitretin and methotrexate for at least eight weeks has been ineffective or not tolerated, unless both are contraindicated.

Product Group	Products	Criteria Requirements
Level 1	- Spevigo (spesolimab-sbzo)	**1.** Diagnostic criteria. **2.** Severity criteria.

Q. Generalized Pustular Psoriasis (GPP) – Provider-administered Products

Spevigo (spesolimab-sbzo) IV or SC may be considered medically necessary when criteria 1 and 2 below are met.

1. **Diagnostic Criteria:** A diagnosis of **generalized pustular psoriasis (GPP)** when established by or in consultation with a specialist in dermatology.
2. **Severity Criteria:** Criterion a or b below are met.
   - **a. Treatment of GPP flare (IV formulation only)** when all of the following are met:
     - **i.** Documentation of disease progression despite usual treatment with cyclosporine OR infliximab unless not tolerated, or both are contraindicated.
     - **ii.** There is involvement of ≥ 5% of body surface area (BSA) with erythema and the presence of pustules.

   OR

   - **b. Maintenance treatment for GPP (SC formulation for loading dose only)** when all of the following are met:
     - **i.** History of at least two moderate-to-severe flares, with at least one associated with fever, elevated C-reactive protein level, elevated white blood cell count, asthenia, or myalgia
     - **ii.** Currently not experiencing a flare
     - **iii.** Treatment with acitretin and methotrexate for at least eight weeks has been ineffective or not tolerated, unless both are contraindicated.

Product Group	Products	Criteria Requirements
Level 1	- Spevigo (spesolimab-sbzo)	**1.** Diagnostic criteria. **2.** Severity criteria.
	- Avsola, Inflectra (infliximab)	Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620
Non-Preferred Infliximab Products	- Infliximab biosimilars (Renflexis, Ixifi) - Remicade (infliximab) - Unbranded Janssen infliximab product	Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620

R. Giant Cell Arteritis (GCA)

1. **Site of Care Requirements:** For provider-administered therapies, site of care administration requirements are met [refer to Medication Policy Manual, Site of Care Review, dru408].
2. **Diagnostic Criteria:** A diagnosis of **giant cell arteritis** (GCA) when established by or in consultation with a specialist in rheumatology (see *Appendix 6*).
3. **Severity Criteria:** Requested medication will be given in combination with high-dose corticosteroids (prednisone 20 to 60 mg per day or equivalent) unless contraindicated or not tolerated.

Product Group	Products	Criteria Requirements
Self-administered Products	- Actemra (tocilizumab) SC	**1.** Diagnostic Criteria **2.** Severity Criteria
Preferred Provider-administered Products	- Actemra (tocilizumab) IV - Tyenne (tocilizumab-aazg) IV	**1.** Site of Care Requirements **2.** Diagnostic criteria **3.** Severity Criteria
Non-Preferred Provider-Administered Products	- Tofidence IV (tocilizumab-bavi)	**1.** Diagnostic Criteria **2.** Severity Criteria **3.** There is a documented intolerance or contraindication to all preferred provider-administered therapies.

S. Hidradenitis Suppurativa (HS) – Self-administered Products		
1. **Diagnostic Criteria:** A diagnosis of **hidradenitis suppurativa** (HS) established by or in consultation with a specialist in dermatology. **2.** **Severity Criteria:** Treatment with at least one conventional agent was not effective after 12 weeks, not tolerated, or all are contraindicated. Conventional agents for the treatment of HS include topical antibiotics, systemic antibiotics (e.g., oral tetracyclines, clindamycin, rifampin, moxifloxacin, metronidazole), intralesional corticosteroids (e.g., triamcinolone), hormonal therapies (e.g., oral contraceptives, spironolactone), cyclosporine, finasteride, metformin, or oral retinoids.		
Product Group	**Products**	**Criteria Requirements**
Level 1	- Cosentyx (secukinumab) - Hadlima (adalimumab-bwwd) - Humira (adalimumab) - Simlandi (adalimumab-ryvk)	**1.** Diagnostic Criteria **2.** Severity Criteria
Non-Preferred Adalimumab Products	- Adalimumab biosimilars (Abrilada, Amjevita, Cyltezo, Hulio, Hyrimoz, Idacio, Yuflyma, Yusimry)	**1.** Diagnostic Criteria **2.** Severity Criteria **3.** There is a documented intolerance or contraindication to **Humira (adalimumab), Hadlima (adalimumab-bwwd), and Simlandi (adalimumab-ryvk).**

T. Hidradenitis Suppurativa (HS) – Provider-administered Products		
1. <u>Site of Care Requirements</u>: For provider-administered therapies, site of care administration requirements are met [refer to Medication Policy Manual, Site of Care Review, dru408]. **2. <u>Diagnostic Criteria</u>:** A diagnosis of **hidradenitis suppurativa** (HS) established by or in consultation with a specialist in dermatology. **3. <u>Severity Criteria</u>:** Treatment with at least one conventional agent was not effective after 12 weeks, not tolerated, or all are contraindicated. Conventional agents for the treatment of HS include topical antibiotics, systemic antibiotics (e.g., oral tetracyclines, clindamycin, rifampin, moxifloxacin, metronidazole), intralesional corticosteroids (e.g., triamcinolone), hormonal therapies (e.g., oral contraceptives, spironolactone), cyclosporine, finasteride, metformin, or oral retinoids.		
Product Group	**Products**	**Criteria Requirements**
Level 1	- Avsola, Inflectra (infliximab)	Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620
Non-Preferred Infliximab Products	- Infliximab biosimilars (Renflexis, Ixifi) - Remicade (infliximab) - Unbranded Janssen infliximab product	Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620

U. Immune-Mediated Colitis		
1. **Diagnostic Criteria:** A diagnosis of **colitis** due to Yervoy (ipilimumab) or an anti-PD1/PD-L1 agent [such as Tecentriq (atezolizumab), Bavencio (avelumab), Libtayo (cemiplimab), Imfinzi (durvalumab), Opdivo (nivolumab), or Keytruda (pembrolizumab)]. 2. **Severity Criteria:** Treatment with an adequate course of corticosteroids (for example, prednisone 40 to 60 mg/day, oral budesonide 9 mg/day, or budesonide rectal for 7 days) has been ineffective or is contraindicated.		
Product Group	**Products**	**Criteria Requirements**
Level 1	- Entyvio (vedolizumab)	**1.** Diagnostic Criteria **2.** Severity Criteria
	- Avsola, Inflectra (infliximab)	Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620
Non-Preferred Infliximab Products	- Infliximab biosimilars (Renflexis, Ixifi) - Remicade (infliximab) - Unbranded Janssen infliximab product	Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620

V. Polyarticular Juvenile Idiopathic Arthritis (PJIA) – Self-administered Products		
1. **Diagnostic Criteria:** A diagnosis of **polyarticular juvenile idiopathic arthritis** (PJIA) established by or in consultation with a specialist in rheumatology. **2.** **Severity Criteria:** Treatment with a csDMARD (such as leflunomide, methotrexate, or sulfasalazine) was ineffective after at least 6 weeks, unless not tolerated or all are contraindicated.		
Product Group	**Products**	**Criteria Requirements**
Level 1	- Enbrel (etanercept) - Hadlima (adalimumab-bwwd) - Humira (adalimumab) - Simlandi (adalimumab-ryvk)	**1.** Diagnostic Criteria **2.** Severity Criteria
Level 2	- upadacitinib (Rinvoq, Rinvoq LQ) - Xeljanz (tofacitinib)	**1.** Diagnostic Criteria **2.** Severity Criteria **3.** Treatment with **ONE Level 1 TNF inhibitor** was not effective after at least a 12-week treatment course unless not tolerated or contraindicated.
Level 3	- Actemra (tocilizumab) SC	**1.** Diagnostic Criteria **2.** Severity Criteria **3.** Treatment with **adalimumab** was not effective after at least a 12-week treatment course unless not tolerated or contraindicated.
Level 4	- Orencia (abatacept) SC	**1.** Diagnostic Criteria **2.** Severity Criteria **3.** There is clinical documentation that treatment with **at least TWO** of the following treatments was not effective after at least a 12-week treatment course unless all were not tolerated or are contraindicated: **a. Humira (adalimumab), Hadlima (adalimumab-bwwd), or Simland (adalimumab-ryvk)** **b. Enbrel (etanercept)** **c. Actemra (tocilizumab) SC**
Non-Preferred Adalimumab Products	- Adalimumab biosimilars (Abrilada, Amjevita, Cyltezo, Hulio, Hyrimoz, Idacio, Yuflyma, Yusimry)	**1.** Diagnostic Criteria **2.** Severity Criteria **3.** There is a documented intolerance or contraindication to **Humira (adalimumab), Hadlima (adalimumab-bwwd), and Simlandi (adalimumab-ryvk).**

Non-Preferred Etanercept Products	- Etanercept biosimilars (Erelzi, Eticovo)	**1.** Diagnostic Criteria **2.** Severity Criteria **3.** There is a documented intolerance or contraindication to **Enbrel (etanercept)**.

W. Polyarticular Juvenile Idiopathic Arthritis (PJIA) – Provider-administered Products		
1. **Site of Care Requirements:** For provider-administered therapies, site of care administration requirements are met [refer to Medication Policy Manual, Site of Care Review, dru408]. **2.** **Diagnostic Criteria:** A diagnosis of **polyarticular juvenile idiopathic arthritis** (PJIA) established by or in consultation with a specialist in rheumatology. **3.** **Severity Criteria:** Treatment with a csDMARD (such as leflunomide, methotrexate, or sulfasalazine) was ineffective after at least 6 weeks, unless not tolerated or all are contraindicated.		
Product Group	**Products**	**Criteria Requirements**
Level 1	- Actemra (tocilizumab) IV - Orencia (abatacept) IV - Simponi Aria (golimumab) IV - Tyenne (tocilizumab-aazg) IV	**1.** Site of Care Requirements **2.** Diagnostic Criteria **3.** Severity Criteria
	- Avsola, Inflectra (infliximab)	Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620
Non-Preferred Infliximab Products	- Infliximab biosimilars (Renflexis, Ixifi) - Remicade (infliximab) - Unbranded Janssen infliximab product	Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620
Non-Preferred Tocilizumab Products	- Tofidence (tocilizumab-bavi) IV	**1.** Site of Care Requirements **2.** Diagnostic Criteria **3.** Severity Criteria **4.** There is a documented intolerance or contraindication to Actemra (tocilizumab) IV and Tyenne (tocilizumab-aazg) IV.

X. Polymyalgia Rheumatica (PMR)
Kevzara (sarilumab) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria 1 and 2 below are met. **1.** Kevzara (sarilumab) will be used for treatment of **polymyalgia rheumatica** (PMR) when established by or in consultation with a specialist in rheumatology. **AND** **2.** One of the following criteria (a or b) are met: **a.** Treatment with an adequate course of corticosteroids (prednisone 15 to 25 mg /day or equivalent) over 4- 6 weeks has been ineffective or is contraindicated. **OR** **b.** The patient has been unable to taper an adequate course of corticosteroids without experiencing worsening of disease.

Y. Psoriatic Arthritis (PsA) – Self-administered Products		
1. <u>Diagnostic Criteria</u>: A diagnosis of **psoriatic arthritis** (PsA) established by or in consultation with a specialist in dermatology or rheumatology.		
Product Group	**Products**	**Criteria Requirements**
Level 1	- Cosentyx (secukinumab) - Enbrel (etanercept) - Hadlima (adalimumab-bwwd) - Humira (adalimumab) - Otezla (apremilast) - Simlandi (adalimumab-ryvk) - Skyrizi (risankizumab-rzaa) - Stelara (ustekinumab) - Tremfya (guselkumab)	**1.** Diagnostic Criteria
Level 2	- Tofacitinib (Xeljanz/Xeljanz XR) - Upadacitinib (Rinvoq, Rinvoq LQ)	**1.** Diagnostic Criteria **2.** Treatment with **ONE Level 1 TNF inhibitor** was not effective after at least a 12-week treatment course unless not tolerated or contraindicated.
Level 3	- Cimzia (certolizumab pegol) syringes - Orencia (abatacept) SC - Simponi (golimumab) SC - Taltz (ixekizumab)	**1.** Diagnostic Criteria **2.** There is clinical documentation that treatment with **at least TWO Level 1 or Level 2** self-administered therapies was not effective after at least a 12-week treatment course unless all were not tolerated or are contraindicated.
Non-Preferred Adalimumab Products	- Adalimumab biosimilars (Abrilada, Amjevita, Cyltezo, Hulio, Hyrimoz, Idacio, Yuflyma, Yusimry)	**1.** Diagnostic criteria **2.** There is a documented intolerance or contraindication to **Humira (adalimumab), Hadlima (adalimumab-bwwd), and Simlandi (adalimumab-ryvk).**
Non-Preferred Etanercept Products	- Etanercept biosimilars (Erelzi, Eticovo)	**1.** Diagnostic criteria **2.** There is a documented intolerance or contraindication to **Enbrel (etanercept)**.

Z. Psoriatic Arthritis (PsA) – Provider-administered Products		
1. **<u>Site of Care Requirements</u>:** For provider-administered therapies, site of care administration requirements are met [refer to Medication Policy Manual, Site of Care Review, dru408]. **2.** **<u>Diagnostic Criteria</u>:** A diagnosis of **psoriatic arthritis** (PsA) established by or in consultation with a specialist in dermatology or rheumatology.		
Product Group	**Products**	**Criteria Requirements**
Level 1	- Cosentyx (secukinumab) IV - Simponi Aria (golimumab) IV - Stelara (ustekinumab)	**1.** Site of Care Requirements **2.** Diagnostic Criteria
	- Avsola, Inflectra (infliximab)	Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620
Level 2	- Cimzia (certolizumab pegol) vials - Orencia (abatacept) IV	**1.** Site of Care Requirements **2.** Diagnostic Criteria **3.** There is clinical documentation that treatment with **at least TWO Level 1** therapies was not effective after at least a 12-week treatment course unless all were not tolerated or are contraindicated.
Non-Preferred Infliximab Products	- Infliximab biosimilars (Renflexis, Ixifi) - Remicade (infliximab) - Unbranded Janssen infliximab product	Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620

AA.	Rheumatoid Arthritis (RA) – Self-administered Products	
1. **<u>Diagnostic Criteria</u>:** A diagnosis of **rheumatoid arthritis** (RA) when established by or in consultation with a specialist in rheumatology (see *Appendix 4*). **2.** **<u>Severity Criteria</u>:** Treatment with a conventional synthetic DMARD (csDMARD) for at least 6 to 12 weeks was ineffective, not tolerated, or all csDMARDs are contraindicated. csDMARDs for RA include hydroxychloroquine, leflunomide, methotrexate, and sulfasalazine.		
Product Group	**Products**	**Criteria Requirements**
Level 1	- Enbrel (etanercept) - Hadlima (adalimumab-bwwd) - Humira (adalimumab) - Simlandi (adalimumab-ryvk)	**1.** Diagnostic Criteria **2.** Severity Criteria
Level 2	- Rinvoq (upadacitinib) - Tofacitinib (Xeljanz/Xeljanz XR)	**1.** Diagnostic Criteria **2.** Severity Criteria **3.** Treatment with **ONE Level 1 TNF inhibitor** was not effective after at least a 12-week treatment course unless not tolerated or contraindicated.
Level 3	- Actemra (tocilizumab) SC	**1.** Diagnostic Criteria **2.** Severity Criteria **3.** Treatment with **adalimumab** was not effective after at least a 12-week treatment course unless not tolerated or contraindicated.
Level 4	- Cimzia (certolizumab pegol) syringes - Kevzara (sarilumab) - Olumiant (baricitinib) - Orencia (abatacept) SC - Simponi (golimumab) SC	**1.** Diagnostic Criteria **2.** Severity Criteria **3.** There is clinical documentation that treatment with **at least TWO Level 1 or 2** therapies was not effective after at least a 12-week treatment course unless all were not tolerated or are contraindicated.
	- Kineret (anakinra)	Refer to Medication Policy Manual, Interleukin-1 Antagonists, dru677
Non-Preferred Adalimumab Products	- Adalimumab biosimilars (Abrilada, Amjevita, Cyltezo, Hulio, Hyrimoz, Idacio, Yuflyma, Yusimry)	**1.** Diagnostic Criteria **2.** Severity Criteria **3.** There is a documented intolerance or contraindication to **Humira (adalimumab), Hadlima (adalimumab-bwwd), and Simlandi (adalimumab-ryvk).**

Non-Preferred Etanercept Products	- Etanercept biosimilars (Erelzi, Eticovo)	**1.** Diagnostic Criteria **2.** Severity Criteria **3.** There is a documented intolerance or contraindication to **Enbrel (etanercept)**.

BB. Rheumatoid Arthritis (RA) – Provider-administered Products		
1. **Site of Care Requirements:** For provider-administered therapies, site of care administration requirements are met [refer to Medication Policy Manual, Site of Care Review, dru408]. **2.** **Diagnostic Criteria:** A diagnosis of **rheumatoid arthritis** (RA) when established by or in consultation with a specialist in rheumatology (see *Appendix 4*). **3.** **Severity Criteria:** Treatment with a conventional synthetic DMARD (csDMARD) for at least 6 to 12 weeks was ineffective, not tolerated, or all csDMARDs are contraindicated. csDMARDs for RA include hydroxychloroquine, leflunomide, methotrexate, and sulfasalazine.		
Product Group	**Products**	**Criteria Requirements**
Level 1	- Simponi Aria (golimumab) IV	**1.** Site of Care Requirements **2.** Diagnostic Criteria **3.** Severity Criteria
	- Avsola, Inflectra (infliximab)	Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620
Level 2	- Actemra (tocilizumab) IV - Cimzia (certolizumab pegol) vials - Orencia (abatacept) IV - Tyenne (tocilizumab-aazg) IV	**1.** Site of Care Requirements **2.** Diagnostic Criteria **3.** Severity Criteria **4.** There is clinical documentation that treatment with **at least TWO Level 1** therapies was not effective after at least a 12-week treatment course unless all were not tolerated or are contraindicated.
Non-Preferred Infliximab Products	- Infliximab biosimilars (Renflexis, Ixifi) - Remicade (infliximab) - Unbranded Janssen infliximab product	Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620
Non-Preferred Tocilizumab Products	- Tofidence (tocilizumab-bavi) IV	**1.** Site of Care Requirements **2.** Diagnostic Criteria **3.** Severity Criteria **4.** There is a documented intolerance or contraindication to Actemra (tocilizumab) IV and Tyenne (tocilizumab-aazg) IV.

CC. Systemic Juvenile Idiopathic Arthritis (SJIA; Still's disease)

1. **Site of Care Requirements:** For provider-administered therapies, site of care administration requirements are met [refer to Medication Policy Manual, Site of Care Review, dru408].
2. **Diagnostic Criteria:** A diagnosis of **systemic juvenile idiopathic arthritis** (SJIA; Still's disease) when established by or in consultation with a specialist in rheumatology.
3. **Severity Criteria:** Both criteria a and b below are met.
   a. There is disease activity greater than 6 weeks.
   AND
   b. One of the following are met (i or ii):
      i. Treatment with at least one oral conventional agent was not effective after 12 weeks, not tolerated, or is contraindicated. Conventional agents for the treatment of SJIA include azathioprine, cyclosporine, leflunomide, methotrexate, systemic corticosteroids, or tacrolimus.
      OR
      ii. Treatment with at least one NSAID (such as ibuprofen, celecoxib) was not effective after 4 weeks, not tolerated, or all are contraindicated.

Product Group	Products	Criteria Requirements
Preferred Provider-administered products	- Actemra (tocilizumab) IV - Tyenne (tocilizumab-aazg) IV	**1.** Site of Care Requirements **2.** Diagnostic Criteria **3.** Severity Criteria
Non-Preferred Provider-Administered Products	- Tofidence IV (tocilizumab-bavi)	**1.** Diagnostic Criteria **2.** Severity Criteria **3.** There is a documented intolerance or contraindication to all preferred provider-administered therapies.
Self-administered Products	- Actemra (tocilizumab) SC	**1.** Diagnostic Criteria **2.** Severity Criteria
	- Kineret (anakinra)	Refer to Medication Policy Manual, Interleukin-1 Antagonists, dru677

DD. Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD)

1. **Diagnostic Criteria:**
   - **a.** The diagnosis has been established by or in consultation with a pulmonologist or rheumatologist.

   AND

   - **b.** Documentation of fibrosis of at least 10% of the lungs on high-resolution computed tomographic scan (HRCT).
2. **Severity Criteria:** Documentation of disease progression despite usual treatment, including both of the following criteria a and b below are met.
   - **a.** At least one immunomodulator/anti-inflammatory used chronically for ILD (such as azathioprine, cyclosporine, tacrolimus, rituximab, cyclophosphamide, mycophenolate mofetil, and/or glucocorticoids) was ineffective, not tolerated, or all are contraindicated.

   AND

   - **b.** Documented disease progression (including but not limited to) one of the following: a decline in forced vital capacity (FVC) of at least 10% in one year, worsening respiratory symptoms, decreased exercise capacity, decline in diffusing capacity of the lungs for carbon monoxide (DLCO) of >15% in one year, worsening on high-resolution computed tomography (HRCT), increased in acute medical care, such as hospitalization, and/or need for supplemental oxygen.

Product Group	Products	Criteria Requirements
Self-administered Products	- Actemra (tocilizumab) SC	**1.** Diagnostic Criteria **2.** Severity Criteria

EE. Takayasu Arteritis

1. **Site of Care Requirements:** For provider-administered therapies, site of care administration requirements are met [refer to Medication Policy Manual, Site of Care Review, dru408].
2. **Diagnostic Criteria:** The diagnosis of **Takayasu arteritis** has been established by or in consultation with a specialist in rheumatology or immunology.
3. **Severity Criteria:** One of following criterion a or b below are met.
   - **a.** The patient has been unable to taper corticosteroids without experiencing worsening of disease (e.g., unable to achieve doses of 15 to 20 mg per day or less of prednisone or equivalent after 8 weeks).

   OR

   - **b.** The patient is experiencing breakthrough disease (for example, relapses or active disease flares) while stabilized on a csDMARD (such as methotrexate, leflunomide, mycophenolate mofetil, azathioprine or cyclophosphamide) for at least 8 weeks.

Product Group	Products	Criteria Requirements
Preferred Provider-administered products	- Actemra (tocilizumab) IV - Tyenne (tocilizumab-aazg) IV	**1.** Site of Care Requirements **2.** Diagnostic Criteria **3.** Severity Criteria
	- Avsola, Inflectra (infliximab)	Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620
Non-Preferred Provider-Administered Products	- Tofidence IV (tocilizumab-bavi)	**1.** Diagnostic Criteria **2.** Severity Criteria **3.** There is a documented intolerance or contraindication to Actemra (tocilizumab) IV and Tyenne (tocilizumab-aazg) IV.
Non-Preferred infliximab Products	- Infliximab biosimilars (Renflexis, Ixifi) - Remicade (infliximab) Unbranded Janssen infliximab product	Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620
Self-administered Products	- Actemra (tocilizumab) SC	**1.** Diagnostic Criteria **2.** Severity Criteria

FF. Transplant (Solid Organ), antibody-mediated rejection (AMR)

Tocilizumab IV may be considered medically necessary when criteria 1 and 2 below are met.

1. **Diagnostic Criteria:** When either criterion a or b below are met.
   a. **Prevention of antibody (Ab)-mediated rejection:** Prior to solid organ transplant and in the peri-operative period, for patients at high risk for Ab-mediated rejection, including highly sensitized patients, and those receiving an ABO-incompatible organ

   OR

   b. **Treatment of antibody-mediated rejection** (a.k.a. vascular rejection, humoral rejection): following solid organ transplant and confirmed by either biopsy or presence of panel reactive antibodies (PRAs).

AND

2. **Severity Criteria:** Treatment with immunoglobulin (IVIG), plasma exchange/pheresis (PLEX), and rituximab has been ineffective or is contraindicated.

Product Group	Products	Criteria Requirements
Level 1	- Actemra (tocilizumab) IV - Tyenne (tocilizumab-aazg) IV	**1.** Diagnostic Criteria **2.** Severity Criteria
Non-Preferred Tocilizumab Products	Tocilizumab biosimilar (Tofidence IV)	**1.** Diagnostic Criteria **2.** Severity Criteria **3.** There is a documented intolerance or contraindication to **all Level 1** therapies.

GG. Ulcerative Colitis (UC) – Self-administered Products		
1. **Diagnostic Criteria:** A diagnosis of **ulcerative colitis** (UC) when established by or in consultation with a specialist in gastroenterology. **2.** **Severity Criteria:** At least one of criterion a, b, or c below, are met. **a.** Treatment with an adequate course of corticosteroids (for example, prednisone 40 to 60 mg/day, oral budesonide 9 mg/day, or budesonide rectal for 7 to 14 days) was ineffective or is contraindicated. **OR** **b.** The patient has been unable to taper an adequate course of corticosteroids without experiencing worsening of disease. **OR** **c.** The patient is experiencing breakthrough disease (for example, active disease flares) while stabilized on a conventional immunomodulators, for at least two months. Conventional immunomodulators for UC include azathioprine, balsalazide, cyclosporine, mercaptopurine, mesalamine, and sulfasalazine.		
Product Group	**Products**	**Criteria Requirements**
Level 1	- Hadlima (adalimumab-bwwd) - Humira (adalimumab) - Simlandi (adalimumab-ryvk) - Stelara (ustekinumab)	**1.** Diagnostic Criteria **2.** Severity Criteria
Level 2	- Simponi (golimumab) SC - Rinvoq (upadacitinib) - Tofacitinib (Xeljanz/Xeljanz XR)	**1.** Diagnostic Criteria **2.** Severity Criteria **3.** Treatment with **adalimumab** was not effective after at least a 12-week treatment course unless not tolerated or contraindicated.
Level 3	- Zeposia (ozanimod)	Refer to Medication Policy Manual, Zeposia, ozanimod, dru674
	- Entyvio (vedolizumab) SC	**1.** Diagnostic Criteria **2.** Severity Criteria **3.** Treatment with **TWO Level 1 or 2 therapies** was not effective after at least a 12-week treatment course unless not tolerated or contraindicated. For members established on Entyvio (vedolizumab) IV therapy, this criterion may be waived.

	- Omvoh (mirikizumab-mrkz) - Velsipity (etrasimod)	**1.** Diagnostic Criteria **2.** Severity Criteria **3.** Treatment with at least **THREE** of the following therapies (i.e., any options listed in a or b below) was not effective after at least a 12-week treatment course unless not tolerated or contraindicated: a. Level 1 options: Hadlima (adalimumab-bwwd), Humira (adalimumab), Simlandi (adalimumab-ryvk) Stelara (ustekinumab) **OR** b. Level 2 options: Rinvoq (upadacitinib), tofacitinib (Xeljanz/Xeljanz)
Non-Preferred Adalimumab Products	- Adalimumab biosimilars (Abrilada, Amjevita, Cyltezo, Hulio, Hyrimoz, Idacio, Yuflyma, Yusimry)	**1.** Diagnostic Criteria **2.** Severity Criteria **3.** There is a documented intolerance or contraindication to **Humira (adalimumab), Hadlima (adalimumab-bwwd), and Simlandi (adalimumab-ryvk).**
Non-Preferred Infliximab Products	- Infliximab products (Zymfentra)	Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620

HH. Ulcerative Colitis (UC) – Provider-administered Products

1. **Site of Care Requirements:** For provider-administered therapies, site of care administration requirements are met [refer to Medication Policy Manual, Site of Care Review, dru408].
2. **Diagnostic Criteria:** A diagnosis of **ulcerative colitis** (UC) when established by or in consultation with a specialist in gastroenterology.
3. **Severity Criteria:** At least one of criterion a, b, or c below, are met.
   - **a.** Treatment with an adequate course of corticosteroids (for example, prednisone 40 to 60 mg/day, oral budesonide 9 mg/day, or budesonide rectal for 7 to 14 days) was ineffective or is contraindicated.

   OR

   - **b.** The patient has been unable to taper an adequate course of corticosteroids without experiencing worsening of disease.

   OR

   - **c.** The patient is experiencing breakthrough disease (for example, active disease flares) while stabilized on a conventional immunomodulators, for at least two months. Conventional immunomodulators for UC include azathioprine, balsalazide, cyclosporine, mercaptopurine, mesalamine, and sulfasalazine.

Product Group	Products	Criteria Requirements
Level 1	- Entyvio (vedolizumab) - Stelara (ustekinumab)	**1.** Site of Care Requirements *(Entyvio only)* **2.** Diagnostic Criteria **3.** Severity Criteria
	- Avsola, Inflectra (infliximab)	Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620
Level 2	- Omvoh (mirikizumab-mrkz)	Refer to coverage criteria for ulcerative colitis (UC) – self-administered products
Non-Preferred Infliximab Products	- Infliximab biosimilars (Renflexis, Ixifi) - Remicade (infliximab) - Unbranded Janssen infliximab product	Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620

II. Uveitis – Self-administered Products

1. **Diagnostic Criteria:** A diagnosis of **uveitis** when established by or in consultation with a specialist in ophthalmology.
2. **Corticosteroid Criteria:** Treatment with corticosteroids (oral, periocular, or intravitreal injections) has been:
   a. Ineffective after two weeks of therapy.
   OR
   b. Unable to be tapered following an adequate course without worsening of disease.
   OR
   c. Not tolerated or all are contraindicated.
3. **Severity Criteria:** Treatment with at least one conventional immunomodulator was not effective after a 6-week treatment course, not tolerated, or all are contraindicated. Conventional immunomodulators for treatment of uveitis include azathioprine, cyclosporine, methotrexate, mycophenolate, or tacrolimus.

Product Group	Products	Criteria Requirements
Level 1	- Hadlima (adalimumab-bwwd) - Humira (adalimumab) - Simlandi (adalimumab-ryvk)	**1.** Diagnostic Criteria **2.** Corticosteroid Criteria **3.** Severity Criteria
Non-Preferred Adalimumab Products	- Adalimumab biosimilars (Abrilada, Amjevita, Cyltezo, Hulio, Hyrimoz, Idacio, Yuflyma, Yusimry)	**1.** Diagnostic Criteria **2.** Corticosteroid Criteria **3.** Severity Criteria **4.** There is a documented intolerance or contraindication to **Humira (adalimumab), Hadlima (adalimumab-bwwd), and Simlandi (adalimumab-ryvk).**

JJ. Uveitis – Provider-Administered Products

1. **Site of Care Requirements:** For provider-administered therapies, site of care administration requirements are met [refer to Medication Policy Manual, Site of Care Review, dru408].
2. **Diagnostic Criteria:** A diagnosis of **uveitis** when established by or in consultation with a specialist in ophthalmology.
3. **Corticosteroid Criteria:** Treatment with corticosteroids (oral, periocular, or intravitreal injections) has been:
   a. Ineffective after two weeks of therapy.

   OR

   b. Unable to be tapered following an adequate course without worsening of disease.

   OR

   c. Not tolerated or all are contraindicated.
4. **Severity Criteria:** Treatment with at least one conventional immunomodulator was not effective after a 6-week treatment course, not tolerated, or all are contraindicated. Conventional immunomodulators for treatment of uveitis include azathioprine, cyclosporine, methotrexate, mycophenolate, or tacrolimus.

Product Group	Products	Criteria Requirements
Level 1	- Avsola, Inflectra (infliximab)	Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620
Non-Preferred Infliximab Products	- Infliximab biosimilars (Renflexis, Ixifi) - Remicade (infliximab) - Unbranded Janssen infliximab product	Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620

KK. Other Immunologic Conditions: Pyoderma gangrenosum, Sarcoidosis		
1. <u>Site of Care Requirements</u>: For provider-administered therapies, site of care administration requirements are met [refer to Medication Policy Manual, Site of Care Review, dru408]. **2. <u>Diagnostic Criteria</u>:** The diagnosis has been established by or in consultation with a specialist in pulmonology, rheumatology, immunology, or other specialist for the disease state. **3. <u>Severity Criteria</u>:** Treatment with a conventional immunomodulator (such as methotrexate, azathioprine, cyclosporine, hydroxychloroquine, leflunomide, or mycophenolate; see *Appendix 3*) was not effective or not tolerated.		
Product Group	**Products**	**Criteria Requirements**
Provider-administered products	- Avsola, Inflectra (infliximab)	Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620
Non-Preferred infliximab Products	- Infliximab biosimilars (Renflexis, Ixifi) - Remicade (infliximab) - Unbranded Janssen infliximab product	Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620

III. Administration, Quantity Limitations, and Authorization Periods

A. Regence Pharmacy Services considers medications in this policy to be self-administered, provider-administered, or either, as listed in **Table 1.**

B. When prior authorization is approved, each drug will be covered in the following quantities and for the following authorization periods outlined in **Table 2.**

C. Unless specifically noted in Table 2, authorization **may** be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective, with documented disease stability or improvement.

Table 1. Administration

Drug	Route	Pharmacy Services considers to be:
Oral administered medications	Oral (PO)	Coverable only under the pharmacy benefit (as a self-administered medication).
Intravenously (IV) administered medications	IV	Coverable only under the medical benefit (as a provider-administered medication).
Subcutaneously (SC) administered medications *(except for those listed below)*	SC	Coverable only under the pharmacy benefit (as a self-administered medication).
Exceptions for the following SC medications:		
Adbry (tralokinumab-ldrm)	SC	Coverable under the pharmacy benefit (as a self-administered medication) OR coverable under the medical benefit (as a provider-administered medication).
Cimzia (certolizumab pegol) lyophilized powder vials	SC	Coverable only under the medical benefit (as a provider-administered medication).
Cimzia (certolizumab pegol) prefilled syringes and pens	SC	Coverable only under the pharmacy benefit (as a self-administered medication).
Cosentyx (secukinumab) prefilled syringes and pens	SC	Coverable only under the pharmacy benefit (as a self-administered medication).
Ilumya (tildrakizumab-asmn)	SC	Coverable only under the medical benefit (as a provider-administered medication).
Skyrizi (risankizumab-rzaa)	SC	Coverable under the pharmacy benefit (as a self-administered medication) OR coverable under the medical benefit (as a provider-administered medication).
Spevigo (spesolimab-sbzo)	SC	Coverable only under the medical benefit (as a provider-administered medication) for GPP **loading dose only** OR coverable under the pharmacy benefit (as a self-administered medication) for GPP **maintenance only.**
Stelara (ustekinumab)	SC	Coverable under the pharmacy benefit (as a self-administered medication) OR coverable under the medical benefit (as a provider-administered medication).

Table 2. Authorization Limits

Product	Route	Authorization Limit
Adbry (tralokinumab-ldrm)	SC	- **AD:** Up to 25 doses (fifty-two 150 mg syringes) in a 48-week period based on dosing of 600 mg at week 0 then 300 mg every other week thereafter (up to fifty-two 150 mg syringes in the first 12-month period followed by forty-eight 150 mg syringes per 12-month period thereafter). - **Pediatric AD (Patients 12 to 17 years):** Up to 25 doses (twenty-six 150 mg syringes) in a 48-week period based on dosing of 300 mg at week 0 then 150 mg every other week thereafter (up to twenty-six 150 mg syringes in the first 12-month period followed by twenty-four 150 mg syringes per 12-month period thereafter).
Tocilizumab (Actemra; biosimilars Tofidence, Tyenne)	IV	- **AMR/Transplant (solid-organ):** Up to 7 infusions (up to 8 mg/kg with an 800 mg per infusion maximum) in a 6-month period based on a recommended infusion interval of every 4 weeks. Authorization shall be reviewed at least every 6 months to confirm that current medical necessity criteria are met, and the medication is effective. - **CRS:** Up to 4 infusions (up to 12 mg/kg). No additional doses will be authorized. - **PJIA:** Up to 13 infusions (up to 10 mg/kg) in a 12-month period based on a recommended infusion interval of every 4 weeks. - **GCA:** Up to 13 infusions (up to 6 mg/kg) in a 12-month period based on a recommended infusion interval of every 4 weeks. - **RA and Takayasu Arteritis:** Up to 13 infusions (up to 8 mg/kg) in a 12-month period based on a recommended infusion interval of every 4 weeks. - **SJIA:** Up to 26 infusions (up to 12 mg/kg) in a 12-month period based on a recommended infusion interval of every 2 weeks.
	SC	- **GCA and Takayasu Arteritis:** Up to 52 syringes in a 1-year period based on a recommended injection interval of 162 mg every week. - **PJIA:** Up to 26 syringes in a 1-year period based on a recommended injection interval of up to 162 mg every two weeks. - **RA:** Up to 52 syringes in a 1-year period based on a recommended injection interval of 162 mg once weekly or every other week. - **SJIA:** Up to 52 syringes in a 1-year period based on a recommended injection interval of 162 mg once weekly. - **SSc-ILD:** Up to 52 syringes in a 1-year period based on a recommended injection interval of 162 mg once weekly.

Product	Route	Authorization Limit
Adalimumab (Humira, biosimilars: Abrilada, Amjevita, Cyltezo, Hadlima, Hulio, Hyrimoz, Idacio, Simlandi, Yuflyma, Yusimry), unbranded: adalimumab-adaz, adalimumab-adbm, adalimumab-ryvk)	SC	- **AS, ERA, PJIA, PsA, RA:** Up to 40 mg every 2 weeks (up to 26 doses in a one-year period). - **HS:** Up to eight 40 mg syringes in the first month based on an initial dose of 160 mg followed by 80 mg on day 15 then 40 mg every week beginning on day 29 (54 syringes in the first 12-month period followed by up to 52 syringes per 12-month period, thereafter). Initial authorization shall be reviewed at 12 weeks to confirm that medication is effective. Thereafter, authorization may be reviewed annually to confirm that current medical necessity criteria are met, and that the medication is effective. - **PsO and Uveitis:** Up to 160 mg (four 40 mg syringes) in the first month based on an initial dose of 80 mg followed by 40 mg every other week (30 syringes in the first 12-month period followed by up to 26 syringes per 12-month period, thereafter). - **CD:** ▪ Up to 12 of the 40 mg syringes in the initial 3-month period; based on a dose of up to 160 mg on day 1, followed by 80 mg on day 15, then 40 mg every other week (31 syringes in the first 12-month period followed by up to 26 syringes per 12-month period, thereafter). ▪ *CD Dose Escalation*: Up to 40 mg every week may be considered medically necessary when there is clinical documentation that current treatment with adalimumab 40 mg every 2 weeks has had an inadequate response after at least a 12-week treatment course (up to 52 syringes per 12-month period). - **UC:** Up to 12 of the 40 mg vials in the initial 3-month period (induction period, per manufacturer labeling), then 40 mg every 2 weeks thereafter (31 syringes in the first 12-month period followed by up to 26 syringes per 12-month period, thereafter). - **Pediatric UC (Patients 5 to 17 years):** Up to 18 of the 40 mg syringes in the initial 3-month period; based on an initial dose of 160 mg on day 1, followed by 80 mg on days 8 and 15, then 80 mg every other week or 40 mg every week beginning on day 29 (58 syringes in the first 12-month period followed by up to 52 syringes per 12-month period, thereafter).
Bimzelx (bimekizumab)	SC	- **PsO:** Up to 320mg (two 160mg syringes/autoinjectors) at weeks 0, 4, 8, 12, and 16, then every 8 weeks thereafter (up to 20 syringes in the first 12-month period followed by up to 14 syringes/autoinjectors per 12-month period thereafter). For patients weighing 120kg or more: up to 320mg (two 160mg syringes/autoinjectors) at weeks 0, 4, 8, 12, and 16, then *every 4 weeks* (up to 28 syringes in the first 12-month period followed by up to 26 syringes/autoinjectors per 12-month period thereafter).[1]
Cibinqo (abrocitinib)	PO	**AD:** Up to 30 tablets per 30 days.
Cimzia (certolizumab pegol)	SC	- **CD, RA, PsA, AS, NR-axSpA:** Up to 3 doses (six 200 mg syringes/vials) in the first month based on an initial dose of 400 mg SC at weeks 0, 2, and 4 followed by 200 mg every two weeks or 400 mg every four weeks for maintenance (27 doses in the first 12-month period followed by up to 26 doses per 12-month period, thereafter). - **PsO:** Up to 400 mg (two 200 mg syringes/vials) every other week (up to 26 doses per 12-month period).

Product	Route	Authorization Limit
Cosentyx (secukinumab)	IV	- **AS, NR-axSpA, and PsA:** Up to 13 infusions (with loading dose: 6 mg/kg at week 0, followed by 1.75 mg/kg every 4 weeks thereafter; without loading dose: 1.75 mg/kg every 4 weeks; both dosing regimens with a maximum maintenance dose 300 mg per infusion).
	SC	- **AS:** Up to 5 doses (five 150 mg syringes or pens) in the first 4 weeks based on a loading dose of 150 mg at weeks 0, 1, 2, 3, and 4, followed by up to 300 mg every 4 weeks thereafter (16 doses in the first 12-month period followed by up to 13 doses per 12-month period, thereafter). - **Nr-axSpA:** Up to 5 doses (five 150 mg syringes or pens) in the first 4 weeks based on a loading dose of 150 mg at weeks 0, 1, 2, 3, and 4, followed by up to 150 mg every 4 weeks thereafter (16 doses in the first 12-month period followed by up to 13 doses per 12-month period, thereafter). - **ERA:** Up to 5 doses (five 150 mg syringes or pens for patients > 50 kg or five 75 mg syringes for patients < 50 kg) in the first four weeks based on dose given at weeks 0, 1, 2, 3, and 4, then every 4 weeks thereafter (150 mg/ dose for patients > 50 kg or 75 mg /dose for patients < 50 kg; 16 doses in the first 12-month period followed by up to 13 doses per 12-month period, thereafter). - **HS:** Up to 5 doses (five 300 mg syringes or pens) in the first 4 weeks based on a loading dose of 300 mg at weeks 0, 1, 2, 3, and 4, followed by up to 300 mg every 4 weeks thereafter (16 doses in the first 12-month period followed by up to 13 doses per 12-month period, thereafter). A dosing interval of every 2 weeks (up to 26 doses per 12-month period) may be considered medically necessary in patients who have had an inadequate response to every 4-week dosing. - **PsA:** ▪ Up to 5 doses (five 150 mg syringes or pens) in the first four weeks based on a loading dose of 150 mg at weeks 0, 1, 2, 3, and 4, then 150 to 300 mg every 4 weeks thereafter (16 doses in the first 12-month period followed by up to 13 doses per 12-month period, thereafter). ▪ Pediatric PsA (Patients 2 to 17 years): Up to 5 doses (five 150 mg syringes or pens for patients > 50 kg or five 75 mg syringes for patients < 50 kg) in the first four weeks based on dose given at weeks 0, 1, 2, 3, and 4, then every 4 weeks thereafter (150 mg/ dose for patients > 50 kg or 75 mg /dose for patients < 50 kg; 16 doses in the first 12-month period followed by up to 13 doses per 12-month period, thereafter). ▪ For patients with both PsA and PsO, dosing for PsO should be used. - **PsO:** ▪ Up to 5 doses (ten 150 mg syringes or pens) in the first four-week period based on dosing of 300 mg at weeks 0, 1, 2, 3, and 4, then up to 300 mg every 4 weeks thereafter (16 doses in the first 12-month period followed by up to 13 doses per 12-month period, thereafter). ▪ Pediatric PsO (Patients 6 to 17 years): Up to 5 doses (five 150 mg syringes or pens for patients > 50 kg or five 75 mg syringes for patients < 50 kg) in the first four weeks based on dose given at weeks 0, 1, 2, 3, and 4, then every 4 weeks thereafter (150 mg/ dose for patients > 50 kg or 75 mg /dose for patients < 50 kg; 16 doses in the first 12-month period followed by up to 13 doses per 12-month period, thereafter).

Product	Route	Authorization Limit
Entyvio (vedolizumab)	IV induction followed by IV maintenance	- **CD and UC:** ▪ Up to 6 doses (six 300 mg infusions) in a 6-month period based on a recommended starting interval of 300 mg infusions at zero, two and six weeks, then every eight weeks thereafter (9 infusions in the first 12-month period followed by up to 7 infusions per 12-month period, thereafter). ▪ Dose escalation: A dosing interval of every 4 weeks (up to 13 infusions per 12-month period) may be considered medically necessary in patients who have had an inadequate response to every 8-week dosing given for at least 24 weeks. Dosing more frequent than every 4 weeks is considered investigational (Table 5 *Investigational Uses: Dosing or Dose Escalation* for more information). ▪ Authorization may be reviewed at least annually and clinical documentation indicating that there is disease stability or improvement must be provided. - **Immune-Mediated Colitis:** Up to 6 doses (six 300 mg infusions) in a 6-month period based on a recommended starting interval of 300 mg infusions at zero, two and six weeks, then every eight weeks thereafter.
	IV induction followed by SC maintenance	- **CD and UC:** Up to 2 doses (two 300 mg infusions) in a 2-month period based on a recommended starting interval of 300 mg infusions at zero and two weeks, then up to 26 doses (twenty-six 108 mg injections) per 12-month period based on maintenance dosing of 108 mg SC every 2 weeks.
Etanercept (Enbrel, biosimilars)	SC	- **AS, ERA, PJIA, PsA, RA:** Up to 50 mg per week given as a single 50 mg dose weekly or 25 mg twice weekly. - **PsO:** Up to 50 mg twice per week for the first 3 months (per manufacturer labeling), then 50 mg per week thereafter given as a single 50 mg dose weekly or 25 mg twice weekly.
Ilumya (tildrakizumab-asmn)	SC	**PsO:** Up to two doses (two 100 mg syringes) in the initial four-week period followed by one dose (one 100 mg syringes) every 12 weeks thereafter based on an initial dose of 100 mg at weeks 0 and 4 followed by maintenance dosing of 100 mg every 12 weeks (up to five 100 mg syringes in the first 12-month period followed by four 100 mg syringes per 12-month period thereafter).
Kevzara (sarilumab)	SC	**PMR, RA:** Up to twenty-six 200 mg syringes in a one-year period based on a dose of 200 mg subcutaneously every two weeks.
Litfulo (ritlecitinib)	PO	**AA:** Up to twenty-eight capsules per 28 days.
Olumiant (baricitinib)	PO	**AA, RA:** Up to thirty 2 mg tablets per 30 days. - *AA Dose Escalation*: Up to 4 mg daily may be considered medically necessary when there is clinical documentation that current treatment with baricitinib 2 mg daily has had an inadequate response (defined as not achieving a SALT score of ≤20 or at least 80% scalp hair coverage) after at least a 9-month treatment course.

Product	Route	Authorization Limit
Omvoh (mirikizumab-mrkz)	IV	**UC:** Up to 3 doses (three 300 mg infusions) in the first 8-week period based on a recommended starting interval of 300 mg infusions at zero, four, and 8 weeks, then up to 12 doses (twenty-four 100 mg SC injections) in the first 12-month period based on a maintenance dose of 200 mg SC given at week 12 and every 4 weeks thereafter.
	SC	**UC:** Up to 13 doses (twenty-six 100 mg injections) per 12- month period based on maintenance dosing of 200 mg SC every 4 weeks.
Orencia (abatacept)	IV	- **aGVHD:** Up to 4 infusions (up to 10 mg/kg) in a 4-week period based on a dose of 10 mg/kg/ dose given on days −1, +5, +14, and +28 post-transplant. - **RA, PJIA PsA:** Up to 3 infusions (up to 1000 mg) in the first 4-week period, based on weight-based loading doses at weeks 0, 2 and 4, followed by maintenance dosing of up to 13 infusions in a 12-month period, based on a dose of one infusion (up to 1000 mg) every 4 weeks (14 infusions in the first 12-month period followed by up to 13 infusions per 12-month period, thereafter).
	SC	- **PJIA:** Up to 52 doses (52 syringes) in a 12-month period, based on a weight-based dose of 50 mg to 125 mg every week. - **PsA:** Up to 52 doses (52 syringes) in a 12-month period, based on a dose of 125 mg every week. - **RA:** Up to 52 doses (52 syringes) in a 12-month period, based on a dose of 125 mg every week. A single IV loading dose (up to 1000 mg) may be authorized, if required.
Otezla (apremilast)	PO	**PsO, PsA, BD:** Up to 60 tablets per 30 days.
Siliq (brodalumab)	SC	**PsO:** Up to 3 doses (210 mg syringes) in the first month based on an initial dose of 210 mg subcutaneously at weeks 0, 1, and 2 followed by 210 mg every 2 weeks thereafter (27 doses in the first 12-month period followed by up to 26 doses per 12-month period, thereafter).
Simponi (golimumab)	SC	- **AS, PsA, RA:** Up to 12 doses (twelve 50 mg syringes) in a 1-year period based on a recommended injection interval of once monthly. - **UC:** Up to 2 doses in the initial four-week period based on a dose of 200 mg at week 0 and 100 mg at week 2, followed by maintenance therapy of 100 mg every four weeks (14 doses in the first 12-month period followed by up to 13 doses per 12-month period, thereafter).

Product	Route	Authorization Limit
Simponi Aria (golimumab)	IV	- **AS, PsA, RA:** Up to 2 infusions (up to 2 mg/kg) in the first 4-week period, based on weight-based loading doses at weeks 0 and 4, followed by maintenance dosing of up to 7 infusions in a 12-month period, based on a dose of one infusion (up to 2 mg/kg) every 8 weeks (8 infusions in the first 12-month period followed by up to 7 infusions per 12-month period, thereafter). - **PJIA:** Up to 2 infusions (up to 80 mg/m2) in the first 4-week period, based on body-surface-area-based loading doses at weeks 0 and 4, followed by maintenance dosing of up to 7 infusions in a 12-month period, based on a dose of one infusion (up to 80 mg/m2) every 8 weeks (8 infusions in the first 12-month period followed by up to 7 infusions per 12-month period, thereafter). - **Dose escalation:** Dosing interval of up to every 6 weeks may be considered medically necessary in patients who have had an inadequate response to every 8-week dosing given for at least 24 weeks. - Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met, and the medication is effective.
Skyrizi (risankizumab-rzaa)	SC (PsA, PsO)	**PsA, PsO:** Up to 2 doses (four 75 mg syringes or two 150 mg syringes) in the initial four-week period followed by 150 mg (two 75 mg syringes or one 150 mg syringe) every 12 weeks based on dosing of 150 mg SC at weeks 0 and 4 followed by maintenance dosing of 150 mg every 12 weeks (up to twelve 75 mg syringes or six 150 mg syringes in the first 12-month period followed by up to ten 75 mg syringes or five 150 mg syringes per 12-month period, thereafter).
	IV Induction (CD)	**CD:** Up to 3 doses (three 600 mg infusions) in the first 8-week period based on a recommended starting interval of 600 mg infusions at zero, four, and 8 weeks, then up to 6 (six 180 mg or 360 mg cartridges) in the first 12-month period based on a maintenance dose of 180 mg or 360 mg given at week 12 and every 8 weeks thereafter.
	SC Maintenance dosing for CD	- **CD:** Up to 7 doses (seven 180 mg or 360 mg cartridges) per 12- month period based on maintenance dosing of 180 mg or 360 mg SC every 8 weeks. - Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met, and the medication is effective.
Sotyktu (deucravacitinib)	PO	**PsO:** Up to thirty tablets per 30 days based on a recommended dose of 6 mg daily.
Spevigo (spesolimab-sbzo)	IV	- **GPP flare:** Up to two 900 mg infusions given within a 4-week approval period, based on a single dose of 900 mg. A second additional 900 mg dose, given one week after the initial dose, may be given once if symptoms persist, within the 4-week approval period. **NOTE:** *No more than two doses are coverable for any one flare.* - For consideration of treatment of a <u>new flare</u> (after at least 4 weeks): Authorization shall be reviewed to confirm that current medical necessity criteria are met, including flare criteria, and that the medication was effective for the previously treated flare. Each additional flare authorization is for a maximum of two 900 mg doses over a 4-week approval period.

<table>
<tr><th>Product</th><th>Route</th><th>Authorization Limit</th></tr>
<tr><td></td><td>SC</td><td>- GPP maintenance when <u>not</u> experiencing a flare: One 600 mg dose (four pre-filled 150 mg syringes) in the initial four-week period followed by 300 mg (two pre-filled 150 mg syringes) every four weeks thereafter.
- GPP maintenance after IV treatment of a flare: Four weeks after treatment with IV Spevigo (spesolimab), up to one 300 mg dose (two 150 mg prefilled syringes) every four weeks thereafter.
- Authorization may be reviewed at least every 6 months to confirm that current medical necessity criteria are met, and the medication is effective.</td></tr>
<tr><td rowspan="3">Stelara (ustekinumab)</td><td>SC (PsO and PsA)</td><td>PsO and PsA:
- For all patients regardless of weight, up to five doses (five 45 mg syringes or vials) in a 48-week period based on dosing of 45 mg at week 0 and 4, then 45 mg every 12 weeks thereafter (up to five 45 mg syringes or vials in the first 12-month period followed by four 45 mg syringes or vials per 12-month period thereafter).
- <u>Dose escalation</u>: For patients in whom the 45 mg dose has shown benefit, but who have not achieved clinical remission after at least a 12-week trial, doses of up to 90 mg every 12 weeks may be considered medically necessary. Dosing more frequent than 90 mg every 12 weeks is considered investigational (see <u>Table 5 Investigational Uses: Dosing or Dose Escalation for more information</u>).</td></tr>
<tr><td>IV Induction (CD and UC Only)</td><td>- CD and UC Only: A single, weight-based IV infusion initially (vials, see chart below for details), then up to 6 doses (six 90 mg syringes or twelve 45 mg vials) based on maintenance dosing of 90 mg SC every 8 weeks. Initial IV dosing is as follows:
<table>
<tr><th>Weight</th><th>Dose</th></tr>
<tr><td>55 kg or less</td><td>260 mg (2 x 130 mg vial)</td></tr>
<tr><td>More than 55 kg to 85 kg</td><td>390 mg (3 x 130 mg vial)</td></tr>
<tr><td>More than 85 kg</td><td>520 mg (4 x 130 mg vial)</td></tr>
</table>
- <u>Additional IV induction courses</u> doses may be considered medically necessary in patients who have previously had an inadequate response to every 8-week dosing given for at least 24 weeks or who have had a break in therapy.</td></tr>
<tr><td>SC Maintenance dosing for CD and UC</td><td>- CD and UC:
▪ Up to 7 doses (seven 90 mg syringes or fourteen vials) in a one-year based on maintenance dosing of 90 mg SC every 8 weeks.
▪ <u>Dose escalation/Re-induction</u>: A dosing interval of up to every 4 weeks be or additional IV doses may be considered medically necessary in patients who have had an inadequate response to every 8-week dosing given for at least 24 weeks. Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met, and the medication is effective.</td></tr>
<tr><td>Taltz (ixekizumab)</td><td>SC</td><td>- PsO: Up to 7 doses (eight 80 mg syringes) in the initial 12-week period based on a dose of 160 mg</td></tr>
</table>

Product	Route	Authorization Limit
		initially at week 0, followed by 80 mg at weeks 2,4, 6, 8, 10, and 12, followed by maintenance dosing of 80 mg every four weeks (up to eighteen 80 mg syringes in the first 12-month period followed by up to thirteen 80 mg syringes per 12-month period, thereafter). - **AS, PsA:** ▪ Up to 13 doses (fifteen 80 mg syringes) in a one-year period based on 160 mg initially at week 0, followed by maintenance dosing of 80 mg every 4 weeks (up to fifteen 80 mg infusions in the first 12-month period followed by up to thirteen 80 mg syringes per 12-month period, thereafter). ▪ For patients with both PsA and PsO, dosing for PsO should be used. - **NR-axSpA:** Up to 13 doses (thirteen 80 mg syringes) in a one-year period a dose 80 mg every 4 weeks.
Tofacitinib (Xeljanz, Xeljanz XR)	PO	- **AS, PsA, RA:** ▪ Xeljanz: Up to sixty 5 mg tablets per 30 days, based on a recommended dose of 5 mg twice daily. ▪ Xeljanz XR: Up to thirty 11 mg tablets per 30 days, based on a recommended dose of 11 mg once daily. - **PJIA:** ▪ Xeljanz Oral Solution: Up to 300 mL of 1 mg/mL oral solution per 30 days, based on a recommended dose of up to 5 mg (5 mL of oral solution) twice daily. ▪ Xeljanz: Up to sixty 5 mg tablets per 30 days, based on a recommended dose of 5 mg twice daily. - **UC:** ▪ Xeljanz: Up to sixty 5 mg or 10 mg tablets per 30 days based on a recommended dose of 5-10 mg twice daily. ▪ Xeljanz XR: Up to thirty 22 mg tablets per 30 days, based on a recommended dose of 22 mg once daily.
Tremfya (guselkumab)	SC	**PsA, PsO:** Up to 2 doses (two 100 mg syringes) in the first 4-week period based on an initial dose of 100 mg SC at weeks 0 and 4, followed by maintenance dosing of 100 mg every 8 weeks (up to eight doses in the first 12-month period followed by up to seven doses thereafter).
Upadacitinib (Rinvoq, Rinvoq LQ))	PO	- **PsA, RA, AS, PJIA, NR-axSpA:** Up to thirty 15 mg tablets per 30 days, based on a recommended dose of 15 mg once daily. - **PsA/PJIA** oral solution 1 mg/mL: up to 360ml per 30 days (based on up to 6 mg twice daily). - **AD:** Up to 30 mg daily per 30 days, based on a recommended dose of up to 30 mg once daily. - **CD:** Up to 45 mg daily per 30 days for 12 weeks, then up to 30 mg daily, based on a recommended dose of up to 30 mg once daily for maintenance. - **UC:** Up to 45 mg daily per 30 days for 8 weeks then up to 30 mg daily, based on a recommended dose of up to 30 mg once daily for maintenance.
Velsipity (etrasimod)	PO	**UC:** Up to 30 tablets per 30 days.

Key: aGVHD: acute graft versus host disease; AD: atopic dermatitis; AMR: antibody mediated rejection; AS: ankylosing spondyloarthritis; BD: Behçet's

disease; CD: Crohn's disease; CRS: cytokine-release syndrome; ERA: enthesitis-related arthritis; GCA: giant cell arteritis; GPP: generalized pustular psoriasis; HS: hidradenitis suppurativa; PJIA: polyarticular juvenile idiopathic arthritis; PMR: polymyalgia rheumatica; NR-axSpA: non-radiographic axial spondyloarthritis; PsA: psoriatic arthritis; PsO: plaque psoriasis; RA: rheumatoid arthritis; SJIA: systemic juvenile idiopathic arthritis; SpA: spondyloarthritis; SSc-ILD: systemic sclerosis-associated interstitial lung disease; UC: ulcerative colitis

IV. Not Medically Necessary Uses

Medications included in this policy are not considered medically necessary when used according to Table 3.

Table 3. Not medically Necessary Uses

Adalimumab	Maintenance doses > 40 mg every 2 weeks for RA	Adalimumab is considered not medically necessary when used in maintenance doses exceeding 40 mg every 2 weeks for rheumatoid arthritis (RA). The benefit of increasing the dose of adalimumab for the treatment of RA from 40 mg every other week to 40 mg weekly as monotherapy is uncertain. [2] - One study reported a modest improvement in ACR50; however, there were not significant improvements in ACR20 or ACR70. - Because the study was not designed to evaluate the comparative effectiveness of higher doses, the comparison between weekly and every other week dosing is exploratory. - As the added benefit of increasing the dose of adalimumab is uncertain, the use of 40 mg weekly is considered not medically necessary.
Unbranded adalimumab-adbm, adalimumab-adaz, adalimumab-ryvk	All uses	The unbranded biosimilars adalimumab-adbm and adalimumab-ryvk manufactured by Quallent Pharmaceuticals and adalimumab-adaz manufactured by Cordavis are considered not medically necessary for all uses.
Etanercept	Maintenance doses > 50 mg per week	Etanercept is considered not medically necessary when used in maintenance doses exceeding 50 mg per week. - There is no data available establishing that therapy with etanercept at a dose of 50 mg twice weekly (beyond 3 months of initial therapy) offers a significant advantage over continued therapy with 50 mg of etanercept weekly. [3 4]
Ilumya (tildrakizumab-asmn)	Doses > 100 mg every 12 weeks	Ilumya (tildrakizumab-asmn) is considered not medically necessary when used in doses exceeding 100 mg every 12 weeks. - Ilumya (tildrakizumab-asmn) is FDA approved for PsO at a dose of 100 mg every 12 weeks. While clinical trials of in PsO evaluated doses 100 mg and 200 mg every 12 weeks, both doses appeared to have similar efficacy. Therefore, the use of doses higher than 100 mg every 12 weeks is considered

		not medically necessary. [5]
Stelara (ustekinumab)	Initial doses of 90 mg for PsO/PsA	Stelara (ustekinumab) is considered not medically necessary at initial doses of 90 mg per every 12 weeks, regardless of weight. - Given that more than half of all patients respond to the 45 mg dose, and the significantly higher cost of 90 mg dosing, a trial of 45 mg for all patients, regardless of weight, represents the best treatment value for PsO/PsA. - When treatment with 45 mg has resulted in some benefit, but has not a clinical remission after at least a 12-week trial, up to 90 mg every 12 weeks may be considered medically necessary. - Dosing was established through a post-hoc analysis of the results of the Phoenix 1 and Phoenix 2 trials. The recommended weight-based dosing scheme was not studied in a prospective manner. [6 7] Patients greater than 100 kg were found to have, on average, a better response to treatment when receiving a dose of 90 mg every 12 weeks compared with 45 mg every 12 weeks. ▪ In Phoenix 1, 68.5% and 54.0% of patients greater than 100 kg achieved PASI75 in the 90 mg and 45 mg groups, respectively. ▪ In Phoenix 2, 71.1% and 49.1% of patients greater than 100 kg achieved PASI75 in the 90 mg and 45 mg groups, respectively. - There is no evidence to support the need for re-induction when the dose is escalated from 45 mg to 90 mg is made.
Olumiant (baricitinib)	Doses > 2 mg daily in rheumatoid arthritis (RA)	Olumiant (baricitinib) is considered not medically necessary when used in doses exceeding 2 mg daily for RA. - Olumiant (baricitinib) is FDA approved for 2 mg daily in RA. - While doses of 4 mg have been shown to be effective, a signal of thromboembolic risk was identified, and the dose was not approved in RA. Further controlled-studies, including a comparative study between the 2 mg and 4 mg, are needed to clarify the risk-benefit profile of the higher dose in RA. [8]
	COVID-19, outpatient use	Olumiant (baricitinib) is considered not medically necessary when used for COVID-19 in the *outpatient* setting. - Olumiant (baricitinib) is FDA approved for the treatment of COVID-19 in *hospitalized* adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) - When used to treat COVID-19, dosing is limited to 14 days or until hospital discharge, whichever occurs first.[9] - There is no available safety and efficacy data supporting the use of baricitinib for COVID-19 in the outpatient setting.

V. Investigational Uses

A. Combination use of targeted DMARDs.

B. Unless otherwise specified in the coverage criteria above, medications included in this policy are considered investigational when used for all other conditions, due to lack of published data, lack of high-quality data, or lack of positive data. Details of select 'Investigational Uses' are listed below in tables 4 and 5.

C. Unless specified in the Administration, Quantity Limitations, and Authorization Periods or as 'Not Medically Necessary Uses' above, all dose escalations above the quantity limit are considered investigational (Additional details are in Table 5).

Table 4: Investigational Uses: Indications

Blau's Syndrome	- There is no reliable evidence to establish the efficacy or safety of targeted DMARDs in the treatment of Blau's syndrome. - No randomized, controlled trials have been published evaluating the use of adalimumab in patients with Blau's syndrome.
Extraintestinal complications of IBD: Arthritis (IBD-associated arthropathy)	- Arthritis is a common extraintestinal complication of IBD (either UC or CD). However, there is no reliable evidence to establish the efficacy or safety of targeted DMARDs in patients with arthritis associated with IBD who do not otherwise require targeted therapy. - The evidence is limited to small, short-term, open-label trials and case studies with infliximab. Given the lack of blinding and lack of control arm, the incremental benefit of infliximab therapy is uncertain. [10] - There are no reliable published clinical trials with any other biologic DMARDs for treatment of arthritis associated with IBD (in the absence of active bowel disease). - Of note: patients with IBD and a confirmed diagnosis of CD or UC with active bowel disease may be covered per the coverage criteria for management of IBD symptoms (active bowel disease). However, the isolated arthritis symptoms (in the absence of active bowel disease) are not coverable.
Graft Versus Host Disease (GVHD)	- There is no reliable evidence to establish the efficacy or safety of targeted DMARDs in the treatment of GVHD. - In one open-label clinical trial (n=62) incidences of GVHD-related mortality, non-relapse mortality, and overall survival were not different between patients treated with infliximab or placebo. [11]
Granuloma Annulare	- There is no reliable evidence to establish the efficacy or safety of targeted DMARDs in the treatment of granuloma annulare. - While case reports have been published describing the treatment of granuloma annulare with etanercept, other reports have been published describing no effect, or an association with the formation of granuloma annulare and treatment with TNF-alfa inhibitors, including etanercept. Additional information is necessary to the benefit of etanercept in this population. [12]
Guttate Psoriasis	- Guttate psoriasis is a type of cutaneous psoriasis. It is characterized by the presence of small, erythematous papules whereas plaque psoriasis is characterized itchy, red, scaly, raised lesions on the skin. Guttate psoriasis is typically managed with topical agents or UV light therapy. - There is no evidence to establish the efficacy or safety of targeted DMARDs in the treatment of guttate psoriasis.
Immune-mediated reactions (other than colitis or CRS with CAR-T cell therapy) due to immunotherapy	- There is no reliable evidence to establish the efficacy of safety of targeted DMARDs in the treatment of immune-mediated reactions, including but not limited to pneumonitis, hepatitis, or arthritis, due to PD-1, PDL-1, or CTLA4 inhibitors. - PD-1, PDL-1, and CTLA4 inhibitors contain warnings for immune-mediated hepatitis. In clinical trials, patients who experienced immune-mediated hepatitis were managed with systemic corticosteroids and mycophenolate. - For immune-mediated hepatitis, NCCN guidelines state that mycophenolate is recommended instead of infliximab due to the concern for hepatotoxicity with infliximab.

Reactive Arthritis/Reiter's Syndrome	- There is no reliable evidence to establish the efficacy or safety of targeted DMARDs in the treatment of reactive arthritis/Reiter's Syndrome.
Sciatica	- There is no reliable evidence to establish the efficacy or safety of targeted DMARDs in the treatment of sciatica. - Evidence for infliximab in the treatment of sciatica is limited to a randomized controlled trial in 40 patients. At 52 weeks, 67% of patients who received infliximab reported no pain compared with 63% of patients who received placebo (p = 0.72). This difference was not statistically significant. [13 14] - There are no randomized controlled trials that evaluate the efficacy and safety of a commercially available formulation of etanercept in the treatment of sciatica. - Evidence for adalimumab in the treatment of sciatica in limited to a small randomized, controlled trial evaluated adalimumab in 61 patients. There was a modest improvement in pain as measured by a 10-point visual analog scale and at three years, the need for back surgery was reduced in adalimumab-treated patients; however, larger clinical trials are needed to confirm the benefit of adalimumab in this population. [15 16]
Scleroderma	- There is insufficient evidence to support the use of tocilizumab for scleroderma. The evidence is limited to one small, placebo-controlled, phase 2 trial using subcutaneous tocilizumab (n=88). The trial found a change in modified Rodan skin score, but no significant difference in skin thickening, disability, fatigue, itching, or patient or clinician global disease severity. Larger Phase 3 trials are needed to establish the safety and efficacy of tocilizumab for scleroderma. [17]
Sjögren's Syndrome	- There is no reliable evidence to establish the efficacy or safety of targeted DMARDs in the treatment of Sjögren's syndrome. - Evidence for etanercept in Sjögren's syndrome is limited a small trial, in which there were no significant differences in the subjective measures of disease severity. [18]
Systemic Lupus Erythematous (SLE)	- There is no reliable evidence to establish the efficacy or safety of targeted DMARDs in the treatment of SLE. - A small uncontrolled clinical trial reported modest efficacy with infliximab in patients with systemic lupus erythematosus, though larger, better designed trials are needed to confirm these results. [19] - A small preliminary study assessing the use of tocilizumab in patients with SLE found promising signs of response, but larger, controlled studies will be needed to establish the efficacy and safety in this population. [20] - One small randomized, placebo-controlled trial evaluated the use of abatacept in patients with non–life-threatening SLE and polyarthritis. The primary endpoint (proportion of patients with a new flare of SLE) was not met but was suggestive of a positive effect in certain exploratory measures. Further study is needed to establish the safety and efficacy of abatacept in SLE. [21] - One 24-week, phase 2 study evaluated the use of baricitinib in patients with SLE. Results demonstrated that baricitinib 4 mg once may reduce SLE disease activity; however, results for the 2 mg dose were not significant. Larger, longer-term studies are needed to clarify the benefit of baricitinib in SLE. [22]

Wegener's Granulomatosis	- There is no reliable evidence to establish the efficacy or safety of targeted DMARDs in the treatment of Wegener's Granulomatosis. - Evidence for infliximab is limited to one small clinical trial in 17 patients. Both infliximab and rituximab appeared to provide benefit in achieving complete or partial response; however, there was a trend favoring rituximab. Additionally, rituximab was better able to maintain remission during the long-term follow-up.

Table 5: Investigational Uses: Dosing or Dose Escalation

Combination use of targeted immunomodulators	- The use of combination (more than one) targeted DMARD therapy, such as Humira (adalimumab), Otezla (apremilast), tofacitinib (Xeljanz/Xeljanz XR), Sotyktu (deucravacitinib), or Entyvio (vedolizumab), is considered investigational (includes all medications included in this policy). *Combination use of apremilast and other targeted immunomodulators:* - There is no reliable evidence to establish the efficacy or safety of the combined use of apremilast and other targeted DMARDs (such as biologics) in the treatment of PsO or PsA. - There are no randomized, controlled trials evaluating the combined use of apremilast and any other targeted DMARD. The evidence is limited to retrospective studies in small numbers of patients. Additional studies are needed to establish long-term efficacy and the overall risk-benefit profile of combination use.
Secukinumab – Maintenance doses higher than 300 mg every 4 weeks for PsA or PsO	- There is insufficient evidence to support the use of secukinumab at maintenance doses higher than 300 mg every 4 weeks for PsO. - Phase 3 clinical trials of secukinumab for PsA and PsO evaluated maintenance dosing regimens of 150 mg or 300 mg every 4 weeks. Higher or more frequent doses have not been evaluated. It is uncertain if there is any additional benefit with increased dosing and the safety profile has not been evaluated.
Secukinumab – Maintenance doses higher than 150 mg every 4 weeks for AS	- There is insufficient evidence to support the use of secukinumab at maintenance doses higher than 150 mg every 4 weeks for AS. - Phase 3 clinical trials of secukinumab for AS evaluated maintenance dosing regimens of 150 mg every 4 weeks. Higher or more frequent doses have not been evaluated. It is uncertain if there is any additional benefit with increased dosing and the safety profile has not been evaluated.
Ustekinumab – Doses higher than 90 mg every 12 weeks for PsO or PsA	- There is insufficient evidence to support the use of ustekinumab at maintenance doses higher than 90 mg every 12 weeks for PsO or PsA. - There are no randomized, controlled trials to support doses higher than 90 mg every 12 weeks in PsO or PsA.
Vedolizumab - Doses higher than 300 mg every 4 weeks	- There is insufficient evidence to support the use of vedolizumab at maintenance doses higher than 300 mg every 4 weeks for CD and UC. - In phase 3 clinical studies of vedolizumab in CD and UC the highest dose of vedolizumab used was 300 mg every four weeks. Higher or more frequent doses have not been evaluated.

Position Statement

- There are many treatments for chronic inflammatory conditions that are effective, have known long-term safety profiles, and are recommended by national treatment guidelines.
- The intent of this policy is to allow coverage of each medication in settings where it has been safe and effective, with coverage after use of lower cost standard of care therapies, including preferred targeted DMARD options.
- Non-medical therapies, such as prescribed exercise therapy, physical therapy, weight loss, and smoking cessation are important treatment plan components for patients suffering from many chronic inflammatory conditions.
- When a systemic medication therapy is needed to manage a chronic inflammatory condition, generic oral therapies usually offer the best value.
- When non-medical therapies and oral medications are inadequate, a targeted DMARD or immunomodulator [conventional synthetic DMARD (csDMARD)] may be appropriate and use is supported by guidelines. Targeted DMARDs include non-biologics and biologics. Biologics include both anti-TNF and non-anti-TNF options.
- When there is no demonstrated difference in safety or efficacy among the studied targeted DMARDs, the medication with the lowest cost often provides the best value for members.
- Individual responses and tolerability of targeted DMARDs, including biologics, are unpredictable and may vary between patients. If one targeted DMARD provides an inadequate response, another targeted DMARD may yet be effective.
- Due to the potential for development of antibodies with anti-TNF therapies which may result in loss of efficacy, clinical practice guidelines generally recommend a trial with one to two anti-TNF therapies. [23-27] For those who have an inadequate response or intolerance to a TNF inhibitor, it is reasonable to consider a targeted treatment with an alternative mechanism of action and proven efficacy for the patient's diagnosis.
- All DMARDs, conventional and targeted, are immunosuppressants and carry a risk of increased infection. Risk and infection type varies by mechanism of action and medication.
- 2021 JAK1/2/3 inhibitors label updates placed their usage after other systemic therapies for the indications in which they have FDA approval due to safety concerns (which include major cardiovascular events and mortality among other concerns).
- There is significant variation in recommended dosing across indications for individual medications, particularly with targeted agents; therefore, when multiple dosage forms of a targeted agent are available, coverage can be provided for those indications where the dosage form has been evaluated in randomized controlled trials, the dosage form has been proven safe and effective, and for which the dosage form has an established dose. For all other indications, the specific dosage form will be considered investigational.
- Inflectra (infliximab-dyyb) and Avsola (infliximab-axxq) are the preferred infliximab products. The reference products and other biosimilars such as Renflexis (infliximab-abda) and Ixifi (infliximab-qbtx) are considered non-preferred. While they share most indications with each other, they are not the preferred formulation of infliximab. Hadlima (adalimumab-bwwd), Humira and

Simlandi (adalimumab-ryvk) are the preferred adalimumab products. The other adalimumab biosimilars such as Abrilada (adalimumab-afzb), Amjevita (adalimumab-atto), Hulio (adalimumab-fkjp), Hyrimoz (adalimumab-adaz), Idacio (adalimumab-aacf), Yuflyma (adalimumab-atty), Yusimry (adalimumab-aqhv), and Cyltezo (adalimumab-adbm) are considered non-preferred. The unbranded biosimilars adalimumab-adbm, adalimumab-ryvk (Quallent Pharmaceuticals), and adalimumab-adaz (Cordavis) are considered not medically necessary. Biosimilars for Enbrel (etanercept) have been approved but none are the preferred formulations for etanercept.

- The medications in this policy, including loading doses, are coverable for the lowest effective doses, aligned with how they were studied in clinical trials, including use of loading doses.

Evidence summary:

Rheumatic Conditions – Background

- Treatments for rheumatic conditions may include non-medical therapies, medications for the management of symptoms, medications that modify the disease course such as conventional synthetic or targeted disease modifying anti-rheumatic drugs (DMARDs).
- Medications to control inflammation such as nonsteroidal anti-inflammatory medications (NSAIDs, e.g., ibuprofen, indomethacin, and naproxen) and glucocorticoids (oral or injected into the joint) are effective for the management of symptoms, particularly during the early stages of disease.
- Generic, conventional synthetic DMARDs (csDMARDs), including methotrexate (MTX), hydroxychloroquine, leflunomide, and sulfasalazine are effective for decreasing symptoms and slowing disease progression, and are recommended by current guidelines.
    * MTX is generally the initial csDMARD for rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA).
    * csDMARDs have known risks. The management of these risks is well established.
- Targeted DMARDs can also decrease symptoms, help preserve joint functioning, and slow the progression of the disease.
- In RA, the best response is seen when targeted DMARDs are used in combination with MTX. ACR Guidelines for the treatment of RA recommend that biologic therapy should be used in combination with methotrexate, when possible, due to increased efficacy over biologic monotherapy. Infliximab and golimumab have been shown to be effective only when used with MTX.
- In JIA, combination therapy with a csDMARD is strongly recommended for infliximab to reduce the risk of anti-drug antibodies against infliximab. [28]

Rheumatic Conditions – Axial Spondyloarthritis (SpA)

- Axial spondylarthritis (SpA) is a form of inflammatory arthritis that includes ankylosing spondylitis (AS) and non-radiographic axial spondylarthritis (nr-axSpA).
- Several targeted DMARDs (as listed in the coverage criteria) have been shown to be effective in the treatment of AS or nr-axSpA.
- There is moderate quality evidence to support the use of targeted DMARDs, particularly TNF inhibitors, in SpA. Clinical trials have consistently shown that treatment with TNF inhibitors reduced disease activity in this population.

- 2019 ACR guidelines for both AS and nr-axSpA recommend TNF inhibitors as the first-line targeted agent. They do not recommend any one TNF inhibitor over another except in patients who also have inflammatory bowel disease or iritis in which case adalimumab or infliximab would be recommended over etanercept. Secukinumab and ixekizumab are recommended as second-line options in patients who have active symptoms without response to a previous TNF inhibitor. TNF inhibitors, secukinumab, or ixekizumab are recommended over tofacitinib in patients with AS. [29]
- Because of similar efficacy among the studied targeted DMARDs, non-preferred/non-formulary options are coverable when preferred/formulary options are ineffective, as detailed in the coverage criteria.

Rheumatic Conditions – Enthesitis-related Arthritis (ERA)

- ERA is a type of juvenile idiopathic arthritis (JIA) that causes swelling or inflammation of the entheses (tendon-to-bone insertion sites).
- 2019 ACR guidelines for Juvenile Idiopathic Arthritis recommend NSAIDs as initial therapy for patients with ERA followed by TNF inhibitors. Methotrexate or sulfasalazine may be used if TNF inhibitors are contraindicated. ACR guidelines have not been updated to include secukinumab.[28]
- There is little comparative evidence to distinguish among the biologic options for ERA due to the lack of head-to-head comparisons.
- The evidence for secukinumab in ERA is based on one small placebo-controlled phase III withdrawal trial that demonstrated a reduced time to disease flare for people on secukinumab versus placebo.[30]

Rheumatic Conditions – Polyarticular Juvenile Idiopathic Arthritis (PJIA); Juvenile Rheumatoid Arthritis (JRA)

- Several targeted DMARDs (as listed in the coverage criteria) have been shown to be effective in the treatment of JIA.
- 2019 ACR guidelines for JIA recommend methotrexate, leflunomide, or sulfasalazine as initial therapy for patients with JIA. Methotrexate is recommended over leflunomide and sulfasalazine due to a larger body of evidence. Biologic agents are recommended in patients who have disease activity despite treatment with methotrexate, sulfasalazine, or leflunomide or in patients with high disease activity or have disease in high-risk joints. [28]
- Combination therapy with a biologic and a csDMARD is recommended to prevent the formation of anti-drug antibodies.
- There is little comparative evidence to distinguish among the targeted options for JIA. Guidelines state that there are mostly equivalent data for safety and efficacy between the biologics and there are lack of head-to-head comparisons between them.
- In patients who have had an inadequate response to a TNF inhibitor, switching to a non-TNF biologic is preferred over a second TNF inhibitor. However, a second TNF inhibitor may be appropriate if patients had a good response to the initial TNF inhibitor. [28]

Rheumatic Conditions – Polymyalgia Rheumatica (PMR)

- The ACR/EULAR guidelines for treatment of PMR recommend treatment with corticosteroids for flare with a long, slow taper. Prior trials in anti TNFI's have been unsuccessful, and trials with treatment with conventional DMARDs have yielded mixed results.

- Sarilumab has demonstrated modest improvement in the ability of patients to maintain sustained remission at one year compared to placebo with a steroid taper.

Rheumatic Conditions – Psoriatic Arthritis (PsA)

- Several targeted DMARDs (as listed in the coverage criteria) have been shown to be effective in the treatment of PsA.
- ACR Guidelines recommend TNF inhibitors as the first-line treatment for PsA. However, other mechanisms can be used in patients with contraindications to TNF inhibitors. The guidelines do not specify the use of any one TNF inhibitor over another. [31]
- In patients who have failed a TNF inhibitor, a second TNF inhibitor is recommend over switching to a different mechanism of action (e.g., an IL-12/23 inhibitor, biologic, IL-17 inhibitors, abatacept, or JAK inhibitor). However, a different mechanism of action may be used in cases of primary TNF inhibitor failure (no response) or a serious adverse event due to a TNF inhibitor. [31]
- Because of similar efficacy among the studied targeted DMARDs, non-preferred/non-formulary options are coverable when preferred/formulary options are ineffective, as detailed in the coverage criteria.

Rheumatic Conditions – Rheumatoid Arthritis (RA)

- Several targeted DMARDs (as listed in the coverage criteria, as well as rituximab) have been shown to be effective in the treatment of RA.
- The efficacy of these targeted DMARDs in the treatment of RA is similar. Guidelines do not recommend one specific targeted DMARD. The initial choice of therapy includes biologic DMARDs (TNF inhibitors or a non-TNF biologic) or targeted synthetic DMARDs (e.g., JAK inhibitors). However, 2021 ACR guidelines have not accounted for recent drug safety communications regarding the risk of serious heart-related events with JAK inhibitors. [32 33]
- In patients who have had an inadequate response to targeted therapy, guidelines recommend switching to a targeted DMARD of a different class rather a different DMARD of the same class. [32]
- Guidelines have recommendations for specific patient populations including non-TNF inhibitors over TNF inhibitors for patients with New York Heart Association (NYHA) class III or IV heart failure. This recommendation is based on the risk of worsening heart failure observed in RCTs of TNF inhibitors in patients with heart failure. [32]
- Because of similar efficacy among the studied targeted DMARDs, non-preferred/non-formulary options are coverable when preferred/formulary options are ineffective, as detailed in the coverage criteria.

Rheumatic Conditions – Systemic Juvenile Idiopathic Arthritis (SJIA)

- Systemic JIA is a subtype of juvenile idiopathic arthritis that is associated with systemic inflammation. [34]
- Systemic JIA is defined as arthritis in at least one joint for at least 6 weeks in patients less than 16 years of age that is accompanied for other systemic manifestation such as erythematous rash, lymphadenopathy, hepatomegaly, or splenomegaly, and serositis. [34]
- Several targeted agents (as listed in the coverage criteria) have been shown to be effective or are recommended by clinical practice guidelines in the treatment of SJIA. [24]

- Due to lack of high-quality data, the comparative efficacy for these agents in the treatment of SJIA is uncertain.
- The efficacy of these targeted DMARDs (as listed in the coverage criteria) in the treatment of SJIA is similar. However, there is a significant difference in the cost between these treatment options. Therefore, the costlier treatment options are coverable only when the less costly options are ineffective.

Rheumatic Conditions – Giant Cell Arteritis (GCA)

- Data evaluating the use of biologic agents in the treatment of GCA is limited; however, there are few treatment options for this condition, which can result in serious complications.
- Subcutaneous tocilizumab in combination with prednisone has been shown to improve remission rates compared to prednisone alone in patients with *newly diagnosed or relapsing* GCA. [35]
- Intravenous tocilizumab is approved for the treatment of GCA; evidence is based primarily on pharmacokinetic exposure data and extrapolation to the efficacy established for subcutaneous tocilizumab in patients with GCA.[36]
- Evidence for the use of TNF inhibitors is lacking, as several small trials have not shown benefit in the treatment of GCA.

Rheumatic Conditions – Behçet's disease

- Evidence for efficacy of apremilast for Behçet's disease (BD) was based on one phase 3, randomized, controlled trial. [37 38] The study included patients who were previously treated with at least one non-biologic therapy and were candidates for systemic therapy. Patients had to have at least two oral ulcers at screening and at least two oral ulcers at randomization. Patients with active major organ involvement were excluded and concomitant treatment for Behçet's disease was not allowed (such as with oral csDMARDs).
- Endpoints were the number of oral ulcer and pain from oral ulcers (rated from 0 to 100).
- At week 12, apremilast significantly improved the daily average number of oral ulcers and reduced pain from oral ulcers. Additionally, higher rates of patients who received apremilast were oral ulcer-free at 12 weeks compared to placebo (53% vs. 22%).

Skin conditions - Atopic Dermatitis (AD)

- AD is a chronic, pruritic inflammatory skin disease. It is often associated with elevated serum immunoglobulin (IgE) levels and a personal or family history of type I allergies, allergic rhinitis, and asthma.
- Treatment guidelines recommend the use of topical corticosteroids and topical calcineurin inhibitors in a step-wise approach, as well as systemic immunosuppressants, such as oral cyclosporine, including when topical therapies are insufficient.
- Clinical studies with systemic biologics were conducted in patients with atopic dermatitis who were not adequately controlled with topical medications.[39-41]
- Based on a recent long-term safety study with tofacitinib there is concern that increases in cardiovascular events, venous thromboembolism, and cancer may be class effects of all JAK inhibitors. Additional long-term controlled safety studies are needed to evaluate these concerns further.

- In comparative trials versus Dupixent (dupilumab), Rinvoq (upadacitinib) showed modest improvements in itchiness and skin clearance[42] but the benefit may be outweighed by potential long-term safety concerns.
- While there are two topical calcineurin inhibitors currently available, topical tacrolimus is indicated for moderate to severe AD whereas Elidel (pimecrolimus) is indicated for mild to moderate disease.
- Goals of treatment include clearance of skin lesions, control of itch, prevention of adverse events and triggers associated with various treatment modalities and preventing future exacerbations.

Skin Conditions – Chronic Plaque Psoriasis (PsO)

- There are many treatments for chronic plaque psoriasis (PsO) that are effective, have known long-term safety profiles, and are recommended by national treatment guidelines.
- Light therapy, including UVB and PUVA, is effective and safe, and PUVA may result in long-term remission. When patients are not able to receive office-administered light therapy, light units for home use may be an appropriate alternative (see Appendix 2 for absolute and relative contraindications for phototherapy/photochemotherapy).
- AAD guidelines (2014) recommend phototherapy after failure of first-line treatment (emollients, topical steroids, and topical calcineurin inhibitors). Most patients with mild-to-moderate psoriasis can achieve adequate control with topical medications or phototherapy.
- When systemic therapy is needed to manage psoriasis, csDMARDs often provide the best value. [43]
    * Conventional synthetic DMARDS (csDMARDs), including MTX, cyclosporine, and Soriatane (acitretin), have a proven track record and have been the standard of care for many years.
    * csDMARDs typically take effect with 6 weeks though some patients may require 12 weeks to have full effect. Among these options, cyclosporine is known to work rapidly.
    * Like all immunosuppressants, including targeted DMARDs, the csDMARDs have known risks. The management of these risks is well established.
- Targeted DMARD may be appropriate for patients with moderate to severe psoriasis (e.g., at least 10% BSA and/or significant pain or functional impairment due to the PsO or when conventional topical or oral therapies, or phototherapy have been inadequate).
- Several targeted DMARDs (as listed in the coverage criteria) have been shown to be effective in the treatment of moderate to severe PsO.
- Within each drug class, efficacy among drugs is similar. In general, when comparing different classes, agents directed against both IL-17A and IL-17F (bimekizumab), IL-17A (ixekizumab and secukinumab) and IL-23 (risankizumab) are more effective at producing skin clearance than TNF inhibitors and other mechanisms of action (PDE-4 inhibitors and tyrosine kinase inhibitors). [43] However, safety is also considered. Despite bimekizumab's head-to-head superiority data compared to ustekinumab, secukinumab and adalimumab, there are concerns for potential for suicidal ideation and behavior and long-term data is lacking. There are several other

agents with good efficacy and established safety.

Skin conditions – Generalized Pustular Psoriasis[44-47]

- GPP is a rare subtype of psoriasis. Flares are characterized by an abrupt onset of widespread painful pustules which can coalesce into larger, "lakes of pus" overlying painful erythema. Significant flares are often accompanied by systemic symptoms, notably fever, general malaise, and extracutaneous manifestations such as arthritis, uveitis, and neutrophilic cholangitis, and may be associated with life-threatening complications,
- Acute flares may be idiopathic or may be triggered by infection, withdrawal, or administration of certain medications (including those used in the treatment of GPP such as corticosteroids, methotrexate, or tumor necrosis factor [TNF] inhibitors), pregnancy, or stress.
- Treatment guidelines recommend the identification and management of potential triggers.
- Choice of therapy depends on disease acuity. Acitretin and methotrexate are the preferred initial treatments for adults with relatively stable GPP due to their relatively slow onset of action. They can be used for long-term maintenance treatment.
- Cyclosporine and infliximab are used for more severe, acute GPP. Cyclosporine or infliximab are often considered first line for severe GPP due to their rapid onset of action. Once control of acute disease is achieved, patients may be maintained on fast-acting therapies or transitioned to acitretin or methotrexate for long-term treatment. There is no comparative data regarding relative efficacies of agents used for GPP.

Skin Conditions – Hidradenitis Suppurativa

- High-quality data evaluating the use of targeted DMARDs in the treatment of hidradenitis suppurativa (HS) are limited; however, there are relatively few treatment options for this condition.
- Although adalimumab is FDA approved for the treatment of HS, infliximab also has data to support use in this indication. [48]
    * A high-quality systematic review showed that weekly-dosed adalimumab improved quality of life in HS compared to placebo; although, the effect size was approximately equal to what is considered a minimally clinically important difference.
    * In the same systematic review, infliximab also improved quality of life compared to placebo, with an effect size well above the threshold for a minimally clinically important difference.
- Trials of adalimumab and secukinumab in HS only included patients with more severe disease, defined as Hurley Stage II or III disease and with at least three abscesses or inflammatory nodules.
- Trials showed that adalimumab significantly improved the hidradenitis suppurativa response rate after 12 weeks of treatment; however, efficacy and safety beyond 12-weeks of treatment has not been established. [49 50]
- Trials showed that secukinumab significantly improved the hidradenitis suppurativa response rate by 16 weeks of treatment.[30]
- Additional long-term randomized controlled trials are needed to understand relative efficacy of other treatments, the safety associated with weekly-dosed adalimumab, and role of oral, non-biologic/non-targeted DMARD treatments for HS.

- Evidence-based guidelines for hidradenitis suppurativa are not available, primarily due to lack of data. However, standard of care therapy reviews suggest the following:
  * Patients may benefit from non-pharmacologic interventions such as good personal hygiene, smoking cessation, and weight-loss.
  * For mild to moderate HS, topical clindamycin and tetracyclines have a proven track record of safety and have been the standard of care.
  * When systemic therapy is needed to manage refractory hidradenitis suppurativa, oral therapies often provide the best value. Options include systemic antibiotics (e.g., oral tetracyclines, clindamycin, rifampin, moxifloxacin, metronidazole), hormonal therapies (e.g., oral contraceptives, spironolactone), cyclosporine, finasteride, metformin, or oral retinoids.

Gastrointestinal conditions –Crohn's Disease (CD) and Ulcerative Colitis (UC)

- There are many treatments for Crohn's disease (CD) and ulcerative colitis (UC) that are effective, have known long-term safety profiles, and are recommended by national treatment guidelines. [51 52]
- Several targeted DMARDs (as listed in the coverage criteria) have been shown to be effective in the treatment of CD and/or UC, for inducing and maintaining remission compared to placebo.
- Due to a lack of head-to head comparative studies, the overall comparative efficacy for these targeted DMARDs in the treatment of CD is uncertain. There is also a lack of comparative evidence for treatment of UC. Therefore, non-preferred/non-formulary options are coverable when preferred/formulary options are ineffective, as detailed in the coverage criteria.
- Although studied in UC, there are no controlled trials of golimumab in CD. Likewise, although studied in CD, there are no controlled trials of certolizumab pegol or natalizumab in UC.
- Restorative proctocolectomy with ileal pouch–anal anastomosis (IPAA) is routinely performed in patients with UC who undergo colectomy. Idiopathic inflammation of the pouch — referred to as pouchitis — is the most common long-term complication of IPAA. Retrospective, uncontrolled studies suggest that TNF antagonists, vedolizumab, or ustekinumab may be effective in the treatment of pouchitis that is refractory to antibiotics.[52]
- Safety considerations:
  * Due to an increased risk of mortality and thrombosis with JAK inhibitors, JAK inhibitors only indicated for patients who have previously had an inadequate response or intolerance to TNF inhibitors.
  * Use of JAK inhibitors should be limited to the shortest duration, with consideration of the benefits and risks for the individual patient. The prescribing information states that the lowest effective dose needed to maintain response should be used.[39 53]

Guidelines: [51] [52 54]

- Lifestyle interventions, such as smoking cessation and diet modification, are important components of a comprehensive treatment plan for patients suffering from CD.

- When medication therapy is needed to manage CD and UC, oral and topical (administered rectally) therapies often provide the best value.
- First-line therapies to induce remission for CD/UC vary, based on severity and anatomic distribution, but may include:
  * Oral corticosteroids, “topical” steroids (enteric-coated budesonide), oral aminosalicylates (5ASAs, such as sulfasalazine or mesalamine). Steroids are used over csDMARDs for induction of remission in moderate to severe UC. Several product formulations are specific to anatomic location of the disease, such as enteric-coated (EC) budesonide or EC mesalamine, or rectal 5ASAs.
  * In addition, topical mesalamine may be used for UC, depending on the extent and location of disease.
  * The use of conventional corticosteroids, such as prednisone, is generally reserved for patients with moderate-to-severe CD/UC refractory to first-line therapies, given the adverse events. Use is generally limited to one to two weeks.
  * Corticosteroids, such as prednisone (40 - 60 mg/day or 1 mg/kg/day), are effective for induction of remission for CD and UC.
- Once remission is induced with corticosteroids, maintenance csDMARD therapy should be initiated. Choice of therapy varies between CD and UC, as well as response to induction therapy(s). Antimetabolite csDMARDs [such as methotrexate (MTX), 6-mercaptopurine (6MP), azathioprine] are slow acting and can take 8 to 12 weeks to have full effect. They are also used to decrease immunogenicity in combination with targeted DMARDs.
- First-line therapies to maintain remission include:
  * CD: 6-mercaptopurine, azathioprine, and methotrexate.
  * UC: oral 5ASAs (e.g., sulfasalazine), topical mesalamine or corticosteroids, or oral corticosteroids, depending on the extent and location of disease.
- When non-medical therapies and oral/topical medications (steroids or aminosalicylates) are inadequate, a targeted DMARD may be appropriate for induction and/or maintenance of disease remission.
- Guidelines for CD list multiple targeted DMARDs as effective treatment options. [51]
  * TNF inhibitors, including infliximab and adalimumab, are recommended in patients who are resistant to corticosteroids or whose disease is refractory to csDMARDs such as azathioprine or 6-mercaptopurine.
  * Ustekinumab is an option for moderate-to-severe CD patients who failed previous treatment with corticosteroids, thiopurines, methotrexate, or anti-TNF inhibitors or who have had no prior exposure to anti-TNF inhibitors.
  * Vedolizumab is also listed as an effective option for the induction and maintenance of remission in CD.
  * Due to the risk of progressive multifocal leukoencephalopathy (PML), a serious (sometimes fatal) adverse event, natalizumab is only recommended after other treatment options have failed.
  * Patients with fistulizing disease and severely active disease may be candidates for initial targeted DMARD. Definitions for

severe disease include the following previous hospitalization for Crohn's disease, extensive anatomic involvement, deep ulcers, prior surgical resection, stricturing and/or penetrating behavior.

- Clinical practice guidelines for the treatment of UC indicate that for patients who initially respond to infliximab but lose response, an increase in dose or shortening of the interval between infusions may improve the likelihood of successful treatment. These guidelines acknowledge that these strategies have not been evaluated in a controlled manner.
- Lack of response and loss of response to TNF inhibitors is common in both CD and UC. The choice of subsequent agent after failure of a TNF inhibitor is typically guided by serum levels. ACG guidelines state that, in patients with adequate serum levels of anti-TNF antibodies switching to another TNF is unlikely to be of benefit.

Gastrointestinal conditions – Immune-mediated Colitis

- Serious or steroid-refractory colitis is a known adverse event associated with checkpoint inhibitors such as ipilimumab, nivolumab, pembrolizumab, atezolizumab, avelumab, cemiplimab, and durvalumab. NCCN guidelines recommend prednisone or methylprednisolone as the first-line treatment for moderate colitis. Infliximab or vedolizumab may be considered if there has been no improvement within 2-3 days of initiating glucocorticoids. [55]
- NCCN guidelines state that the duration of therapy with TNF-inhibitors is not clearly defined but is usually a single dose though a second dose may be required. [55]
- There is not an FDA approved dose for vedolizumab when used for immune-mediate colitis. However, a retrospective analysis identified that most patients required between one and four doses to achieve resolution. [56 57]

Gastrointestinal conditions – Collagenous Colitis

- The European Guidelines on Microscopic Colitis (including lymphocytic colitis and collagenous colitis) recommend budesonide as front line for both induction as well as maintenance in some cases. Evidence for use of second-line therapies in patients with microscopic colitis is scarce and based primarily on case reports. Guidelines support the use of TNF inhibitors and vedolizumab for refractory microscopic colitis. TNF inhibitors, including infliximab and adalimumab, have been reported to induce remission. Vedolizumab has been associated with clinical remission based on case reports; almost all patients were refractory to prior TNF inhibitors; however, no randomized control trials have been published to date.[58]

<u>Other Immunologic Conditions</u>

Acute Graft Versus Host Disease (aGVHD)[59]

- Graft versus host disease (GVHD) is a common complication of allogeneic hematopoietic cell transplant (HCT) that occurs when the graft (donor) cells identify the transplant recipient cells (host) as foreign and initiates an immune reaction that may lead to organ damage or death.
- The risk for GVHD is higher when receiving a HCT from an unrelated donor.

- There are no standard guidelines for prophylaxis of acute GVHD, protocols vary by transplant center. The choice of therapy may depend on the underlying disease, degree of HLA disparity, conditioning regimen, and patient characteristics. Several regimens include a calcineurin inhibitors (tacrolimus, cyclosporine) given with either methotrexate or mycophenolate mofetil. Post-transplantation with cyclophosphamide or T-cell depletion is also used.
- At 6 months post-transplant, abatacept was shown to increase acute GVHD free survival as well as improve overall survival when used for patients with 8/8 HLA matched or 7/8 HLA mismatched unrelated donor HCT when used in combination with a calcineurin inhibitor plus methotrexate.[60]

Alopecia areata (AA)

- Alopecia areata (AA) is a chronic, autoimmune disorder that targets hair follicles, leading to nonscarring hair loss; it causes both hair shedding and inhibition of hair regrowth. The condition most commonly presents on the scalp but may also occur in other hair-bearing areas, such as the eyebrows, eyelashes, beard, and extremities.[61]
- The evidence for baricitinib in AA is based on two double-blind, randomized, placebo-controlled trials in patients with at least 50% scalp hair loss for more than 6 months. In both trials, the proportion of patients who achieved at least 80% scalp hair coverage at week 36 (the primary endpoint) in the baricitinib arms were significantly more than the placebo arms.[9]
- The evidence for ritlecitinib in AA is based on one randomized, double-blind, placebo-controlled trial. Only patients with at least 50% scalp hair loss with no signs of terminal hair regrowth within 6 months were included in the trial. The proportion of patients who achieved at least 80% scale hair coverage at week 24 (primary endpoint) was significantly more in the ritlecitinib arm than placebo arm.[62]
- The Alopecia Areata Consensus Expert guidelines support the use of corticosteroids, topical immunotherapy and conventional (which may include diphenylcyclopropenone [DPCP] or squaric acid dibutyl ester [SADBE]), or oral immunosuppressants (methotrexate, azathioprine, cyclosporine), noting time to effect may take several weeks to months.[63]
- Coverage for stimulation of hair growth is defined by contract language.

Antibody Mediated Rejection of Transplant (solid-organ)[64 65]

- Acute allograft (organ) rejection may be cellular (T-cell mediated) or humoral (antibody-mediated) (AHR, AMR).
- Pre-treatment (desensitization) may reduce the risk of AMR in highly sensitized renal transplant patients.
- Acute humoral rejection (AHR) is also an AMR and can occur outside of the peri-operative period, but most commonly within 6 months after transplant. The diagnosis is confirmed by a renal biopsy.
- The goal of therapy is early antibody elimination with IVIG, pheresis, or a combination of modalities. However, evidence for therapies used in AMR are generally of low quality and protocols vary between transplant centers. PLEX and IVIG are generally regarded as a standard of care for acute active AMR. Rituximab has also been suggested as a treatment option by KDIGO guidelines.[64]

- One study assessed the use of tocilizumab as rescue therapy in 36 kidney transplant patients with chronic AMR who failed standard-of-care treatment with IVIG and rituximab, with or without plasma exchange. Tocilizumab was administered as 8 mg/kg monthly, with a maximal dose of 800 mg for 6 to 25 months. Graft- and patient- survival rates were 80% and 91% at six years post treatment, respectively.[66]
- In a small pilot study (N=10), patients who did not respond to desensitization with IVIG and rituximab (+/- plasma exchange) who were given tocilizumab 8 mg/kg on day 15 then monthly for 6 months with IVIG had a decrease in donor specific antibodies.[67]

Coronavirus-19 (COVID-19)[68 69]

- Baricitinib is FDA-approved for the treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) when used to treat COVID-19. Dosing is limited to 14 days or until hospital discharge, whichever occurs first.[9]
- The evidence for baricitinib in COVID-19 is based primarily on two, large, randomized control trials in hospitalized COVID-19 patients requiring oxygen support. Although the compositive endpoint of progression and mortality was no different between baricitinib or placebo when added to standard of care, there was a statistically significant difference in mortality between groups. When compared to remdesivir alone, baricitinib plus remdesivir reduced the time to recovery as well as composite endpoint of progression or death. However, applicability is limited as patients were not on standard of care corticosteroids. Patients in the trial stopped baricitinib upon discharge or after 14 days, whichever occurred first.
- There is no available safety and efficacy data supporting the use of baricitinib in COVID-19 in the outpatient setting.

Cytokine Release Syndrome (CRS)

- Tocilizumab IV is FDA-approved for the treatment of cytokine release syndrome associated with the use of chimeric antigen receptor (CAR) T cell therapy, such as Kymriah (tisagenlecleucel) and Yescarta (axicabtagene ciloleucel). It is given as a one-time weight-based dose but up to three additional doses may be administered if there is no clinical improvement.
- Subcutaneous tocilizumab and sarilumab, another IL-6 inhibitor, have not been studied in cytokine release syndrome.

Pyoderma Gangrenosum [70 71]

- Pyoderma gangrenosum (PG) is a rare ulcerative skin condition that is often associated with underlying systemic disease.
- First-line options for PG typically are systemic corticosteroids, cyclosporine, or tacrolimus. Infliximab is considered a second-line option when there has been an inadequate response to first-line therapy.
- Infliximab or other targeted DMARD therapy may be used when there is an underlying co-diagnosis of an inflammatory condition, such as ulcerative colitis.

Sarcoidosis

- Sarcoidosis is a multisystem granulomatous disorder characterized by the presence of granulomas in involved organs. It most commonly impacts the lungs and lymph nodes but may manifest in other organs. [72]

- Corticosteroid therapy is used as the primary treatment. Second-line medication options are considered for patients with corticosteroid-refractory disease, and include csDMARDs such as azathioprine, methotrexate, and leflunomide. Targeted DMARD therapy with infliximab is reserved for patients who have not responded to prior csDMARDs. [72 73]

Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD)

- SSc-ILD is an autoimmune condition characterized by immune dysregulation, vasculopathy, and overproduction of collagen. This leads to leading to skin and internal organ fibrosis and thickening of the pulmonary interstitium.
- Establishing an accurate diagnosis of ILD is very important, since misdiagnosis can lead to inappropriate therapy. In general, the diagnosis of interstitial lung disease (idiopathic or due to underlying lung disease) can be made with a high degree of confidence in patients with a compatible clinical presentation and typical high-resolution computed tomography (HRCT) findings.
- Cyclophosphamide, mycophenolate, and other immunomodulators are recommended as initial therapy. Mycophenolate mofetil is often preferred in practice as it has comparable benefit to cyclophosphamide but has a better toxicity profile. Escalation of therapy to biologic or targeted therapy is recommended if there is an inadequate treatment response to initial therapies.[74 75]
- Actemra (tocilizumab) has been shown to slow the rate of decline in pulmonary function in patients with SSc-ILD. While promising, additional data on survival, hospitalization, and quality of life is needed.[36]
- Intravenous administration of Actemra (tocilizumab) is not approved for SSc-ILD. [36]

Takayasu arteritis

- Takayasu arteritis is a rare type of vasculitis where inflammation damages the aorta. Takayasu arteritis is complex and requires specialist management to accurately diagnosis and manage the condition.
- High dose corticosteroids in combination with csDMARDs are recommend as the initial treatment. Targeted DMARD therapy with tocilizumab or infliximab is recommended as second-line options in patients with persistent symptoms despite combination therapy of corticosteroids with a csDMARD, as well as for patients who are unable to taper off corticosteroids. [76]
- Tocilizumab has been evaluated at doses of 8 mg/kg intravenously every 4 weeks or 162 mg subcutaneously weekly. There is limited information on the efficacy of higher doses. [76-79]

Uveitis [80]

- Corticosteroids are the mainstay of therapy in uveitis. Guidelines recommend a high dose course (prednisone 1 mg/kg/day or up to 60-80 mg per day) for up to one month.
- A csDMARD is recommended if there is no response, or worsening, after two to four weeks of steroids. American Academy of Ophthalmology (AAO) guidelines recommend mycophenolate mofetil, azathioprine, methotrexate, cyclosporine, or tacrolimus. There is insufficient comparative evidence to conclude superiority of one csDMARD over another.

- Targeted DMARDs are recommended in patients who have had an inadequate response to corticosteroids and csDMARDs.
    * Adalimumab is FDA approved for uveitis and recommended as a treatment option in AAO guidelines. Adalimumab has been shown to lower flare rates and loss of visual acuity in two phase 3 RCTs in patients with active uveitis despite high-dose corticosteroids.
    * Infliximab is also a recommended treatment option for uveitis based on evidence from several comparative, open-label trials.

Safety Considerations

- In general, the overall safety profiles of targeted DMARDs for chronic inflammatory diseases is favorable. However, several have warnings related to infection risk and hypersensitivity reactions. [51 81-83] All are immunosuppressants and increase the risk of infection, though some drugs may increase the risk more than others.
- Certain products have unique safety concerns that should be factored into the overall risk-benefit profile.
- Oral JAK1/2/3 inhibitors (tofacitinib, upadacitinib, baricitinib, and abrocitinib) contain a boxed warning for increased risk of serious infections, mortality, malignancies, major adverse cardiovascular events, and thrombosis. In a post-marketing safety study, tofacitinib did not meet its primary endpoint of non-inferiority for risk of cardiovascular events and malignancy. Results showed that patients who received tofacitinib at either 5 mg or 10 mg twice daily had a higher rate of cardiovascular events and malignancy compared to patients who received a TNF inhibitor. Though the study only evaluated tofacitinib the warning has been extended to other JAK1/2/3 inhibitors used in the treatment of RA and other inflammatory diseases. [33 53 84-86]
    * The boxed warning is based on a safety study designed to evaluate the safety of tofacitinib relative to TNF inhibitors. The study included patients aged 50 or older with at least one CV risk factor and all patients received background MTX. Patients were randomized to one of three groups: tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, or a TNF inhibitor.
    * The study failed to meet its pre-specified safety endpoint of non-inferiority to TNF inhibitors for risk of cardiovascular events and malignancy.
    * The prescribing information for each JAK1/2/3 inhibitor has been updated to clarify that each JAK1/2/3 inhibitor is only indicated for to certain patients who have not responded or cannot tolerate one or more TNF blockers.[53]
    * The FDA continues to investigate these safety concerns and will provide updates as additional information becomes is available.
    * The risks and benefits of JAK1/2/3 inhibitors in patients at risk for venous thromboembolism should be carefully considered when choosing treatment strategies.
- JAK1/2/3 inhibitors have boxed warnings describing an increased risk of thrombosis. Due to this risk, the use of JAK1/2/3 inhibitors is limited to patients who have failed prior treatment options. There are several alternative targeted agents for the treatment of RA that do not carry a risk for VTE and have longer records of safety experience with comparable or better efficacy than baricitinib. [33]

- While newer agents such as IL-23 inhibitors and IL-17 inhibitors, have demonstrated favorable risk-benefit profiles in clinical studies there is limited long-term safety experience. Additionally, there is limited evidence directly comparing to existing standards of care. [51 81-83]
- New or worsening heart failure is listed as a warning and precaution for TNF inhibitors. A clinical trial evaluating etanercept for the treatment of heart failure was terminated early due to lack of efficacy and suggested higher morality in etanercept-treated patients compared to placebo. Post-market, new or worsening heart failure have been reported with TNF inhibitors.

Dose Escalation

- There are no randomized, controlled trials to support dose escalation of ustekinumab from every 8 to 12 weeks to every four-week dosing in any condition. It is uncertain if there is any additional benefit with increased dosing and there is limited long-term safety data.
  * The evidence supporting the use of every four-week dosing in CD is limited to retrospective, observational studies. [87 88] While some patients experienced disease remission, high-quality, prospective studies are needed to identify the ideal population and clarify the risk-benefit profile. Due to limited evidence supporting use, more frequent dosing of ustekinumab for CD is limited to patients who have had an inadequate response to every 8-week dosing.
  * There are no high-quality studies evaluating the use of every 4-week dosing of ustekinumab in PsO.
  * Additional studies are also needed to clarify the role of dose escalation versus standard dosing or other mechanisms of action.
- Guidelines do not currently support the use of therapeutic drug monitoring of ustekinumab to guide dose escalation.
  * There is very limited evidence on the efficacy of different maintenance troughs for ustekinumab. [89 90]
  * While therapeutic drug monitoring may play a role in the management of TNF inhibitors, the same concepts may not apply to ustekinumab due to its different mechanism of action and pharmacokinetic properties.
- Phase 3 clinical trials of vedolizumab for UC and CD included maintenance dosing intervals of every 4 weeks and every 8 weeks (with a dose of 300 mg). The results demonstrated that the two maintenance doses produce similar response rates. In long-term extension studies some patients who had an inadequate response to every 8-week dosing were able to achieve a response or regain response after increasing to every 4-week dosing. Therefore, the use of every 4-week dosing is limited to patients who have lost response or have had an inadequate response to every 8-week dosing.
- In PsO, there was no statistically significant difference in response for patients who were dose escalated to secukinumab 300 mg every 2 weeks vs every 4 weeks in patients who had suboptimal response to standard dosing at 16 weeks. After 16 weeks, most patients who continued with a 4-week dosing interval were able achieve response.[91]
- Pharmacokinetic and exposure-response modeling suggest shortening the dosing interval for golimumab IV to every 6 weeks may ameliorate waning efficacy toward the end of the standard 8-week dosing interval experienced by a small proportion of patients.[92]

Appendix 1: Relative Potencies of Topical Corticosteroids [93]

Class	Drug	Dosage Form	Strength (%)
Very High Potency	Augmented betamethasone dipropionate	Ointment	0.05
	Clobetasol propionate	Cream, foam, ointment	0.05
	Diflorasone diacetate	Ointment	0.05
	Halobetasol propionate	Cream, ointment	0.05
High Potency	Amcinonide	Cream, lotion, ointment	0.1
	Augmented betamethasone dipropionate	Cream	0.05
	Betamethasone dipropionate	Cream, foam, ointment, solution	0.05
	Desoximetasone	Cream, ointment	0.25
	Desoximetasone	Gel	0.05
	Diflorasone diacetate	Cream	0.05
	Fluocinonide	Cream, gel, ointment, solution	0.05
	Halcinonide	Cream, ointment	0.1
	Mometasone furoate	Ointment	0.1
	Triamcinolone acetonide	Cream, ointment	0.5
Medium Potency	Betamethasone valerate	Cream, foam, lotion, ointment	0.1
	Clocortolone pivalate	Cream	0.1
	Desoximetasone	Cream	0.05
	Fluocinolone acetonide	Cream, ointment	0.025
	Flurandrenolide	Cream, ointment	0.05
	Fluticasone propionate	Cream	0.05
	Fluticasone propionate	Ointment	0.005
	Mometasone furoate	Cream	0.1
	Triamcinolone acetonide	Cream, ointment	0.1
Lower Medium Potency	Hydrocortisone butyrate	Cream, ointment, solution	0.1
	Hydrocortisone probutate	Cream	0.1
	Hydrocortisone valerate	Cream, ointment	0.2
	Prednicarbate	Cream	0.1
Low Potency	Alclometasone dipropionate	Cream, ointment	0.05
	Desonide	Cream, gel, foam, ointment	0.05
	Fluocinolone acetonide	Cream, solution	0.01
Lowest Potency	Dexamethasone	Cream	0.1
	Hydrocortisone	Cream, lotion, ointment, solution	0.25, 0.5, 1
	Hydrocortisone acetate	Cream, ointment	0.5-1

Appendix 2: Absolute and Relative Contraindications for Phototherapy/Photochemotherapy

History of melanoma or squamous-cell carcinoma
History of photosensitivity
Increased risk of photosensitivity due to concomitant disease state (e.g., porphyria, systemic lupus erythematosus) or chronic medication use (e.g., tetracycline or sulfonamide antibiotics)
Physical inability to stand for the required exposure time
Presence of premalignant lesions (e.g., actinic keratosis)
Presence of psoriatic arthritis
Treatment of facial or scalp lesions
Treatment of lesions in the groin area
Treatment of lesions on the palms of the hands or soles of the feet, or on nail beds
Type 1 or type 2 skin

Appendix 3: Select List of Conventional Synthetic Disease Modifying Anti-Rheumatic Drugs (csDMARDs)

csDMARDS for Rheumatic, Skin Conditions, and Uveitis	
Azathioprine (AZA; Imuran)	Methotrexate (oral, injectable)*
Cyclosporine (CSA; Gengraf, Neoral, Sandimmune)*	Mycophenolate (MMF; CellCept, Myfortic)
Hydroxychloroquine (HCQ; Plaquenil)	Sulfasalazine (SSZ; Azulfidine)
Arava (leflunomide)	Soriatane (acitretin) *
csDMARDs for Gastrointestinal conditions	
Azathioprine (AZA; Imuran)	Mercaptopurine (6-MP; Purinethol)
Balsalazide (Colazal, Giazo)	Mesalamine (Apriso, Asacol HD, Delzicol, Lialda, Pentasa)
Cyclosporine (CSA; Gengraf, Neoral, Sandimmune)	Sulfasalazine (SSZ; Azulfidine)

*: Medications used in the treatment of dermatologic conditions

Appendix 4: American College of Rheumatology (ACR) Classification Criteria for Establishing the Diagnosis of Rheumatoid Arthritis (RA) [94 95]

Diagnosis of RA requires the presence of at least 4 of 7 criteria below:	
1.	Morning stiffness in and around joints lasting more than 1 hour.
2.	Arthritis in at least 1 area in a wrist or proximal interphalangeal (PIP) joint (hands or fingers) for > 6 weeks.
3.	Simultaneous swelling or fluid accumulation in 3 or more joints for > 6 weeks.
4.	Symmetric (bilateral joint) involvement for > 6 weeks.
5.	Presence of rheumatoid nodules.
6.	Positive serum rheumatoid factor.
7.	Radiographic changes typical of RA (erosion or unequivocal bony decalcification in or adjacent to the involved joint) on hand and wrist present.

Appendix 5: American College of Rheumatology (ACR) Assessment Components for Improvement in Rheumatoid Arthritis (RA) [96]

-	Tender joint count.
-	Swollen joint count.
-	Patient's assessment of pain.
-	Patient's global assessment of disease activity.
-	Physician's global assessment of disease activity.
-	Patient's assessment of physical function.
-	Acute phase reactant measures (erythrocyte sedimentation rate or C-reactive protein levels).

Appendix 6: American College of Rheumatology (ACR) Classification Criteria for Establishing the Diagnosis of Giant Cell Arteritis (GCA)

Diagnosis of GCA requires the presence of at least 3 of 5 criteria below:	
1.	Morning stiffness in and around joints lasting more than 1 hour.
2.	New onset of localized headache.
3.	Temporal artery tenderness or decreased temporal artery pulse.
4.	Erythrocyte sedimentation rate of 50 mm per hour or greater.
5.	Abnormal temporal artery biopsy.

Cross References
BlueCross BlueShield Association Medical Policy, 5.01.15 - Off Label Use of Infliximab. [April 2023]
Immune Globulin Replacement Therapy (IVIG, SCIG), Medication Policy Manual, Policy No. dru020
Medications for multiple sclerosis, Medication Policy Manual, Policy No. dru753
Site of Care Review, Medication Policy Manual, Policy No. dru408
Dupixent, dupilumab, Medication Policy Manual, Policy No. dru493
Chimeric Antigen Receptor (CAR) T-cell Therapies, Medication Policy Manual, Policy No. dru523
Interleukin-1 Antagonists, Medication Policy Manual, Policy No. 677
Products with Therapeutically Equivalent Biosimilars/Reference Products, Medication Policy Manual, Policy No. dru620

Codes	Number	Description
HCPCS	J3262	Injection, tocilizumab (Actemra IV), 1 mg
HCPCS	J0717	Injection, certolizumab pegol (Cimzia lyophilized powder vials), 1 mg
HCPCS	J3380	Injection, vedolizumab (Entyvio), 1 mg
HCPCS	J3245	Injection, tildrakizumab (Ilumya), 1 mg
HCPCS	J0129	Injection, abatacept (Orencia), 10 mg
HCPCS	J1602	Injection, golimumab (Simponi Aria), 1 mg, for intravenous use
HCPCS	J2327	Injection, risankizumab-rzaa (Skyrizi), intravenous, 1 mg
HCPCS	J1747	Injection, spesolimab-sbzo (Spevigo), 1 mg
HCPCS	J3358	Ustekinumab (Stelara), for intravenous injection, 1 mg
HCPCS	J3357	Ustekinumab (Stelara), for subcutaneous injection, 1 mg

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Revision History

Revision Date	Revision Summary
6/20/2024	Effective 10/1/2024 • Added new Spevigo (spesolimab) SC formulation for maintenance treatment of generalized pustular psoriasis (GPP). • Added biosimilar Simlandi (adalimumab-ryvk) to policy as preferred. • Added unbranded products adalimumab-adbm, adalimumab-ryvk (Quallent Pharmaceuticals), and adalimumab-adaz (Cordavis) to policy as not medically necessary. • Added Tofidence IV (tocilizumab-bavi) to policy as non-preferred. • Added Tyenne IV (tocilizumab-aazg) to policy as preferred. • Added Entyvio SC (vedolizumab) to policy as non-preferred (Level 3) self-administered option for Crohn's disease (CD). • Updated Entyvio SC (vedolizumab) criteria for ulcerative colitis (UC) after two Level 1 or 2 alternatives (previously required three Level 1 or 2 alternatives). • Added Rinvoq (upadacitinib) as a Level 2 product for polyarticular juvenile idiopathic arthritis (PJIA), a new FDA indication. • Added Rinvoq LQ (upadacitinib) new oral solution to policy at parity with Rinvoq.
3/21/2024	Effective 7/1/2024 • Changed Amjevita (adalimumab-atto) [all NDCs] from preferred to non-preferred adalimumab product. • Changed Sotyktu (deucravacitinib) from a Level 3 to a Level 2 self-administered option for chronic plaque psoriasis. • Added Omvoh (mirikizumab-mrkz), Velsipity (etrasimod), and Entyvio SC (vedolizumab) to policy as non-preferred (Level 3) self-administered options for ulcerative colitis (UC). The provider-administered loading doses for Omvoh will follow coverage of the self-administered product. • Added Bimzelx (bimekizumab-bkzx) to policy as a non-preferred (Level 4) self-administered option for chronic plaque psoriasis. • Updated to reflect Avsola (infliximab-axxq) as a preferred infliximab product and Zymfentra (infliximab-dyyb) as a non-preferred infliximab product (for Crohn's disease and ulcerative colitis). • Updated background to include pouchitis and collagenous colitis. • Added Cosentyx (secukinumab) for treatment of hidradenitis suppurativa. • Updated Adbry (tralokinumab) atopic dermatitis age restriction from 18 years of age to 12 years of age based on FDA age expansion. • Updated cross references to include Medications for multiple sclerosis, dru753 and removed both Zeposia (ozanimod), dru674 and Tysabri (natalizumab), dru111 which were both moved to dru753.

Revision Date	Revision Summary
12/7/2023	Effective 1/1/2024 • Added Litfulo (ritlecitinib) to policy for alopecia areata (AA). • Modified criteria for Olumiant (baricitinib) to allow coverage for alopecia areata (AA) • Added new Cosentyx (secukinumab) IV formulation to policy criteria and QL for AS, nrSpA, and PsA. • Removed Cosentyx (secukinumab) lyophilized powder vials for subcutaneous administration as these vials were discontinued. • Made Cibinqo (abrocitinib) a Level 1 treatment option for atopic dermatitis at parity with Adbry (tralokinumab-ldrm) and Rinvoq (upadacitinib)
09/14/2023	Effective 12/1/2023: • Added non-preferred biosimilar Yuflyma (adalimumab-aaty) to the policy. • Modified the QL for SC Actemra (tocilizumab) for treatment of SJIA.
6/1/2023	Effective 7/1/2023: • Modified Cibinqo (abrocitinib) coverage in atopic dermatitis to include ages down to 12 years. • Add preferred adalimumab biosimilars: Hadlima (adalimumab-bwwd), and the Amjevita (adalimumab-atto) biosimilars with NDCs beginning with 55513. • Added Kevzara (sarilumab) to policy for polymyalgia rheumatica (PMR) as a level 1 option. • Added Rinvoq (upadacitinib) to policy for Crohn's disease as a level 2 option.
12/9/2022	Effective 1/19/2023: • Added Spevigo (spesolimab-sbzo) to the policy for generalized pustular psoriasis (GPP) as a provider-administered option. • Added Sotyktu (deucravacitinib) to policy for plaque psoriasis (PsO) as a level 3 self-administered option. • Skyrizi (risankizumab-rzaa) quantity limit updated to include new 180 mg maintenance dose for Crohn's Disease (CD). • Rinvoq (upadacitinib) added to policy for non-radiographic axial spondyloarthritis (Nr-axSpA) as a level 2 self-administered option. Taltz (ixekizumab) product group renamed level 3 (previously named level 2) in Nr-axSpA.
8/29/2022	Effective 10/1/2022: • Modified Rinvoq (upadacitinib) and Xeljanz/Xeljanz XR (tofacitinib) for ulcerative colitis (UC) to be level 2 self-administered options. • Added Skyrizi (risankizumab-rzaa) to policy for Crohn's Disease (CD) as a level 1 self-administered and provider-administered option. • Modified step therapy criteria for level 2 self-administered options for Crohn's Disease (CD). • Added Olumiant (baricitinib) to policy for COVID-19 as not medically necessary (NMN) when used in the outpatient setting. • Added Olumiant (baricitinib) to policy for alopecia areata (AA) as a cosmetic contract exclusion.

Revision Date	Revision Summary
5/23/2022	Effective 6/14/2022: • Removed Kineret (anakinra) and infliximab products from Table 2. • Updated policy formatting and added HCPCS codes for provider-administered products. • Added Rinvoq (upadacitinib) to policy for ulcerative colitis (UC) as a level 3 option. • Added Rinvoq (upadacitinib) to policy for ankylosing spondylitis (AS) as a level 2 option. • Added Adbry (tralokinumab-ldrm) to policy for atopic dermatitis (AD) as a level 1 option. • Added Cibinqo (abrocitinib) to policy for atopic dermatitis (AD) as a level 2 option. • Added Actemra (tocilizumab) IV to policy for Giant Cell Arteritis (GCA). • Updated policy to allow dosing escalation of Simponi Aria (golimumab) to every 6 weeks. • Updated Entyvio (vedolizumab) for Crohn's Disease (CD) to a level 1 option.
2/22/2022	Effective 3/13/2022: • Added Rinvoq (upadacitinib) to policy for psoriatic arthritis (PsA) as a level 2 option. • Added Skyrizi (risankizumab-rzaa) to policy for psoriatic arthritis (PsA) as a level 1 option. • Added tofacitinib (Xeljanz/ Xeljanz XR) to policy for ankylosing spondylitis (AS) as a level 2 option. Cimzia (certolizumab pegol) syringes. • Simponi (golimumab) SC, and Taltz (ixekizumab) were moved to level 3. • Added coverage criteria for Rinvoq (upadacitinib) for atopic dermatitis (AD). • Added coverage criteria for Enbrel (etanercept), Humira (adalimumab), Cosentyx (secukinumab), and Simponi (golimumab) for enthesitis-related arthritis (ERA). • Added coverage criteria for intravenous Actemra (tocilizumab) for solid organ transplant, antibody mediated rejection (AMR). • Added criteria to allow coverage of intravenous Orencia (abatacept) for prophylaxis of graft versus host disease (GVHD). • Yusimry (adalimumab-aqvh) added to policy as a non-preferred adalimumab product. • Wording for intravenous Actemra (tocilizumab) criteria for cytokine release syndrome (CRS) was modified to allow for coverage as part of CAR-T treatment plan. • Updated position statement to clarify that non-TNFs may be an option for New York Heart Association (NYHA) class III/IV heart failure (HF) based on guidelines and post-market reports of new or worsening HF with TNF inhibitors.

Revision Date	Revision Summary
10/15/2021	Effective 1/1/2022: • Revised nomenclature for preferred and non-preferred products. • Updated step therapy requirements for Rinvoq (upadacitinib) and Xeljanz (tofacitinib) for rheumatoid arthritis. • Clarified dosing of Cosentyx (secukinumab). • Added coverage criteria for Actemra (tocilizumab) for Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD). • Updated step therapy requirements for Siliq (brodalumab). • Updated preferred infliximab products. • Added Janssen (infliximab) to policy as non-preferred. • Clarified dosing and uses for Cosentyx (secukinumab) vials.
7/19/2021	Effective 10/1/2021: • Moved Kineret (anakinra) from this policy to new combination Interleukin-1 Antagonists policy (dru677). • Simplified severity criteria for rheumatoid arthritis (RA). Removed specific ineffectiveness requirements. • Updated diagnostic requirements for systemic juvenile idiopathic arthritis (SJIA). Now require disease activity for at least 6 weeks instead of 6 months. • Updated Skyrizi (risankizumab-rzaa) quantity limits for newly available 150 mg syringes.
4/21/2021	• Reformatted policy. • Added Otezla (apremilast) to the policy and archived its standalone policy (dru342 Otezla, apremilast). • Added coverage criteria for Kineret (anakinra) for Deficiency of the Interleukin-1–Receptor Antagonist (DIRA). • Added coverage criteria for sarcoidosis and Takayasu Arteritis. • Clarified that combination therapy with any targeted immunomodulator is considered investigational. • Updated investigational uses. • Updated quantity limits for pediatric ulcerative colitis.
1/20/2021	• Added coverage criteria for Xeljanz (tofacitinib) in PJIA. Updated quantity limits to include Xeljanz (tofacitinib). • Added coverage criteria for Entyvio (vedolizumab) in immune-mediated colitis. • Clarified definition of investigational uses. • Remove term “Preferred” in criterion “P” table to limit confusion with trade. • Split “non-preferred” criteria for self-administered UC drugs into separate criterion for Xeljanz and Simponi.

Revision Date	Revision Summary
10/28/2020	Effective 1/1/2021: • Revised step therapy requirements: - Taltz (ixekizumab) no longer requires a trial of Cimzia (certolizumab pegol) for AS. - Tremfya (guselkumab) is now considered a preferred product for PsA. - Actemra (tocilizumab) now requires step therapy with adalimumab for PJIA and RA. - Enbrel (etanercept) is now considered a preferred medication for chronic plaque psoriasis (PsO). - Stelara (ustekinumab) is now considered a preferred product for UC (self-administered and provider-administered). - Entyvio (vedolizumab) is now considered a preferred provider-administered product for UC. • Added Hulio (adalimumab-fkjp) to policy. • Added Simponi Aria as a preferred provider-administered option for polyarticular juvenile idiopathic arthritis (PJIA), a newly approved FDA indication. • Increased authorization limit for infliximab in immune-mediated colitis to two infusions.

8/25/2020	Effective 10/1/2020: • Separated AS, HS, PJIA, and uveitis sections into separate provider-administered and self-administered sections. • Revised clinical documentation requirements. • Updated quantity limits for Cimzia (certolizumab pegol), Taltz (ixekizumab), and Cosentyx (secukinumab) based on newly FDA approved indications. • Removed references to appendix 3 in policy criteria and listed requirements for prior conventional therapies directly in criteria. • Ankylosing spondylitis: - Cimzia and Simponi will continue to require step therapy through two preferred products. - Taltz will now require step therapy through three preferred products. • Non-Radiographic Axial Spondyloarthritis: - New diagnosis category in policy. - Non-preferred products (e.g., Taltz) will require step therapy through two preferred products. • Chronic Plaque Psoriasis: - Non-biologic-step-therapy requirements changed from "BSA ≥ 10% AND phototherapy AND conventional DMARD" to "BSA ≥ 10% OR phototherapy OR conventional agent." - Conventional agent list expanded from just DMARDs to also include treatments such as topical corticosteroids. - Enbrel will no longer be a preferred product and will require step therapy with Humira (unless the patient is under 18 years of age). - Siliq and Cimzia will now only require step therapy with two preferred products. • **Crohn's Disease:** Self-administered Cimzia will require step therapy with Humira specifically. • Hidradenitis Suppurativa - Removed requirement for disease severity. - Removed requirement for functional impairment. - Expanded list of acceptable step therapies from only antibiotics to also include corticosteroids, hormonal therapies, metformin, and retinoids. • Polyarticular Juvenile idiopathic Arthritis - Actemra SC will require step therapy with Humira specifically. - Orencia SC will require step therapy with Humira, Enbrel, and Actemra specifically. • Psoriatic Arthritis: - Xeljanz will now be a preferred product. - Added Tremfya as a non-preferred product. • **Rheumatoid Arthritis:** Actemra and Xeljanz will now be preferred products. • **Systemic juvenile idiopathic arthritis:** Expanded list of acceptable step therapies from only conventional DMARDs to

Revision Date	Revision Summary
	also include NSAIDs. • **Ulcerative Colitis:** Self-administered Stelara will no longer be a preferred product and will require step therapy with Humira. • **Uveitis:** Expanded list of acceptable step therapies from only systemic corticosteroids to also include periocular intravitreal corticosteroids.
4/22/2020	• Added continuation of therapy (COT) criteria. • Added Avsola (infliximab-axxq) and Abrilada (adalimumab-afzb) to policy. • Updated quantity limits for Cosentyx (secukinumab) in axial Spondyloarthritis/ankylosing spondylitis. • Updated dosing for Xeljanz XR (tofacitinib) in ulcerative colitis. • Clarified criteria for preferred provider-administered options for ulcerative colitis.
10/23/2019	• Rinvoq (upadacitinib) has been added as a preferred self-administered option for RA (new FDA approval). • Simponi (golimumab) has been changed to a non-preferred product for AS, PsA, RA, and UC. • Taltz (ixekizumab) has been added as a non-preferred option for axial Spondyloarthritis/ankylosing spondylitis (new FDA indication). • Stelara (ustekinumab) has been added as a preferred option for UC. • Actemra (tocilizumab) subcutaneous and intravenous dosing has been revised to match the prescribing information. • Removed site of care requirements for immune-mediated colitis, as an acute management indication. • Clarified Olumiant (baricitinib) quantity limits to state 30 tablets per 30 days.
7/24/2019	• Dosing and quantity limits have been simplified and reformatted. • Skyrizi (risankizumab-rzaa) has been added as a preferred self-administered option for plaque psoriasis. • Tremfya (guselkumab) is now preferred for psoriasis. • Entyvio (vedolizumab) now requires prior of one preferred option instead of two when used for CD. • Clarified timeframe for an adequate trial of csDMARDs in multiple indications. • Added atopic dermatitis as an investigational use for Olumiant (baricitinib). • Clarified requirements for Humira (adalimumab) and Enbrel (etanercept) biosimilars. • Simplified requirements for Actemra (tocilizumab) in GCA. • Removed requirement that csDMARDs are given with targeted agents for RA. • Reformatted investigational and NMN use sections (no changes to intent).
5/7/2019	Removed Xeljanz (tofacitinib) step therapy for psoriatic arthritis (PsA) and rheumatoid arthritis (RA). Added to list of non-preferred options for PsA and RA.

Revision Date	Revision Summary
11/16/2018	• Clarified investigational dosing for Cosentyx (secukinumab). • Added coverage criteria for Cimzia (certolizumab pegol) as non-preferred, provider-administered option for PsO. • Clarified that any dose escalation above the quantity limit is considered investigational, unless listed in coverage criteria.
8/17/2018	• Updated indications for Cimzia (certolizumab pegol), Taltz (ixekizumab), and tofacitinib (Xeljanz/Xeljanz XR). • Updated Actemra (tocilizumab) dosage forms and indications to match prescribing information. • Added coverage criteria for Ilumya (tildrakizumab-asmn) as a non-preferred, provider-administered option for PsO. • Added coverage criteria for Olumiant (baricitinib) as a non-preferred, self-administered option for RA. • Updated coverage criteria for infliximab biosimilars to state that they must meet all criteria for the reference product and there must be a documented contraindication or intolerance to the reference product. • Added additional criteria for severe CD. • Clarified reauthorization requirements for adalimumab when used for HS. • RA: Clarified that targeted agents must initially be administered with a csDMARD. • UC: Aligned criteria for steroids and csDMARDs for provider-administered and self-administered sections. • Updated nomenclature for each drug class. • Clarified that provider-administered medications may be reviewed for continued authorization. • Added coverage criteria for pyoderma gangrenosum.
3/1/2018	Added Cimzia (certolizumab pegol) to the site of care program.
2/1/2018	• Updated indications for Simponi Aria (golimumab) and Orencia (abatacept). • Revised dosing intervals for Entyvio (vedolizumab). • Added coverage Actemra (tocilizumab) for cytokine release syndrome due to with chimeric antigen receptor T cell therapy. • Clarified that use of Stelara (ustekinumab) every four weeks is considered investigational. • Clarified that the use of multiple courses of Stelara (ustekinumab) IV loading doses for Crohn's disease is considered investigational.
1/1/2018	• Updated preferred and non-preferred products for all indications. • Removed Otezla (apremilast) from policy. • Clarified Cosentyx (secukinumab) dosing.

Revision Date	Revision Summary
8/11/2017	• Added coverage criteria for Kevzara (sarilumab), as a non-preferred self-administered option for RA. • Added coverage criteria for subcutaneous Actemra (tocilizumab) for GCA. • Added coverage criteria for Orencia (abatacept) for PsA and updated JIA coverage criteria to include SC dosing. • Added coverage criteria for Tremfya (guselkumab), as a non-preferred self-administered option for PsO. • Added Renflexis (infliximab-abda) to policy. • UC: revised step therapy requirements for Entyvio (vedolizumab).
5/12/2017	• Added coverage criteria for Siliq (brodalumab), as a non-preferred self-administered option for PsO. • Clarified step therapy for "self-administered UC treatments." • Updated dose and quantity limits for Taltz (ixekizumab) and Cosentyx (secukinumab). • Added the following as investigational uses: - Scleroderma (any branded medication). - Use of Otezla (apremilast) in combination with targeted immunomodulators for any indication.
12/16/2016	• Updated preferred and non-preferred products for all indications. • Added Inflectra (infliximab-dyyb) to policy. • Updated investigational uses. • CD: Added Stelara (ustekinumab) and revised quantity limits for infliximab. • UC: Revised quantity limits for infliximab.
4/8/2016	• AS: added Cosentyx (secukinumab), changed to diagnosis to axial SpA. • PsO: added Taltz (ixekizumab), updated step therapy requirements nonpreferred drugs. • Added criteria for Giant Cell Arteritis and Hidradenitis Suppurativa. • PsA: Updated step therapy requirements for non-preferred drugs, added secukinumab. • Updated language for combination uses with an oral DMARD for infliximab and golimumab (IV). • Added Xeljanz XR to policy. • Updated investigational uses.
1/8/2016	Updated formatting of biologics policies, consolidating into a single policy for chronic inflammatory diseases.

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Medication Policy Manual | **Policy No:** dru445

Topic: Imlygic, talimogene laherparepvec | **Date of Origin:** February 12, 2016

Committee Approval Date: September 14, 2023 | **Next Review Date:** 2024

Effective Date: December 1, 2023

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Imlygic (talimogene laherparepvec) is an oncolytic immunotherapy indicated for the treatment of unresectable melanoma lesions in patients with recurrent melanoma after initial surgery. Imlygic (talimogene laherparepvec) is injected directly into melanoma lesions by a healthcare provider in a clinic setting.

Policy/Criteria

Most contracts require pre-authorization approval of Imlygic (talimogene laherparepvec) prior to coverage.

I. Continuation of therapy (COT): Imlygic (talimogene laherparepvec) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Imlygic (talimogene laherparepvec) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A through D below are met.

A. A diagnosis of recurrent, unresectable, advanced melanoma (stage III or stage IV-M1a). If disease is metastatic (stage IV-M1a), the metastases only involve sites on the skin, subcutaneous tissue, or lymph nodes.

AND

B. The patient is not immunocompromised (including chronic use of antivirals, systemic corticosteroids at doses of >10 mg prednisone or equivalent, or any medications causing bone marrow suppression).

AND

C. Imlygic (talimogene laherparepvec) is used after initial surgical treatment for melanoma.

AND

D. Imlygic (talimogene laherparepvec) will be used as monotherapy.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Imlygic (talimogene laherparepvec) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Imlygic (talimogene laherparepvec) will be covered in quantities as follows:

1. **Initial Authorization:** Imlygic (talimogene laherparepvec) may be covered in quantities up to 48 mL per 6 months.

2. **Continued Authorization:** Imlygic (talimogene laherparepvec) may be covered in quantities up to 48 mL per 6 months.

C. Authorization shall be reviewed as follows to confirm that the current medical necessity criteria are met, and that the medication is effective.

1. Initial authorization shall be reviewed at 6 months.

2. Continued authorization or re-authorization (after the initial 6-month period) shall be reviewed every 6 months. Clinical documentation (including, but not limited to chart notes) must indicate that there is a partial or complete tumor response (reduction in lesion size) and the absence of visceral organ metastases.

IV. Imlygic (talimogene laherparepvec) is considered not medically necessary when used for all other conditions, including but not limited to:

A. Early-stage melanoma (stage I or II).

B. Cosmetic indications.

V. Imlygic (talimogene laherparepvec) is considered investigational when used for all other conditions, including but not limited to:

A. Metastatic melanoma with systemic disease or visceral metastases (stage IV-M1b or stage IV-M1c).

B. Breast cancer.

C. Squamous cell carcinoma of the head and neck (SCCHN).

D. Pancreatic cancer.

E. Use in combination with any other anticancer therapies.

Position Statement

Summary

- Imlygic (talimogene laherparepvec) is used for the treatment of melanoma lesions when there is recurrence of the melanoma after initial resection. It is injected directly into the lesion by a trained healthcare provider.
- The intent of this policy is to cover Imlygic (talimogene laherparepvec) for the indication and regimen for which it has been shown to be safe and effective, as detailed in the coverage criteria.
- One study found that patients (stage IIIB, IIIC, and IV-M1a) treated with Imlygic (talimogene laherparepvec) had a decrease in melanoma lesion size compared to patients treated with granulocyte macrophage colony-stimulating factor (GM-CSF). [1]
- Imlygic (talimogene laherparepvec) has not been shown to improve overall survival or prevent metastasis of disease. Additionally, it has not been shown to provide any benefit in patients with disease that has spread to internal organs.
- Patients who have problems with their immune system or are required to use medications that affect their immune system should not take Imlygic (talimogene laherparepvec). Since Imlygic (talimogene laherparepvec) has not been studied in these patients, the safety in this population is uncertain and there is an increased risk of severe infection. [2]
- Imlygic (talimogene laherparepvec) has not been studied in combination with other therapies. The safety and effectiveness of combination treatment is uncertain.
- The safety and effectiveness of Imlygic (talimogene laherparepvec) in conditions other than melanoma has not been studied.
- The recommended dose of Imlygic (talimogene laherparepvec) is an initial dose of up to 4 mL of a 10^6 PFU/mL injection, followed by a second dose of up to 4 mL of a 10^8 PFU/mL injection in three weeks. Subsequently, the recommended dose is up to 4 mL of a 10^8 PFU/mL injection every two weeks. The safety and effectiveness of higher doses has not been established. [2]

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations

are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.

- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy

- The safety and efficacy of Imlygic (talimogene laherparepvec) was investigated in one open-label trial (OPTiM trial) in patients with stage IIIB, IIIC, or IV, unresectable melanoma. Patients were randomized to receive either Imlygic (talimogene laherparepvec) or GM-CSF (Leukine [sargramostim]) for 24 weeks, or until there were no remaining lesions that qualified for continued treatment. [1,3]
    * Among Imlygic (talimogene laherparepvec)-treated patients, 16% achieved durable response (complete or partial response maintained continuously for at least 6 months), compared to 2.1% among GM-CSF-treated patients. [1,2]
    * Efficacy is based on shrinking cutaneous lesions, a surrogate endpoint.
    * Imlygic (talimogene laherparepvec) failed to show improvement in overall survival based on pre-specified primary analysis in the clinical trial. [1,3]
- The National Comprehensive Cancer Network (NCCN) guidelines for melanoma lists Imlygic (talimogene laherparepvec) as a recommended option for the local treatment of lesions in patients with stage III and stage IV-M1a disease. [4]

Not Medically Necessary Uses

- There is a lack of evidence that Imlygic (talimogene laherparepvec) is safer or more effective than other treatments for stage I and II melanoma such as chemotherapies, systemic immunotherapies, or targeted therapies.
- The use of Imlygic (talimogene laherparepvec) for cosmetic indications is considered not medically necessary.

Investigational Uses

- A subgroup analysis of the open-label OPTiM trial found no difference in DRR or OS for patients who were treated with Imlygic (talimogene laherparepvec) compared to patients in the control arm if they had stage IV-M1b and stage IV-M1c melanoma. There is no evidence that Imlygic (talimogene laherparepvec) has an effect on systemic disease or visceral metastases. [1]
- A small, phase 2 study evaluated Imlygic (talimogene laherparepvec) as a neoadjuvant therapy (prior to surgical resection) in patients with resectable stage IIIB/IIIC-IVM1a cutaneous melanoma. The primary endpoint was relapse-free survival (RFS). RFS has not been shown to positively correlate with clinically relevant outcomes such as overall

survival or quality of life. Use of Imlygic (talimogene laherparepvec) in the neoadjuvant setting is considered investigational. It is currently approved for use and covered in this population in the adjuvant setting (after surgery). [5]

- Imlygic (talimogene laherparepvec) has not been studied in patients with less common types of melanoma, including primary ocular or mucosal melanoma. [2]
- Imlygic (talimogene laherparepvec) is currently being studied in other cancers. There is no reliable evidence (well-designed, randomized, double-blinded trials) supporting its use in cancers other than melanoma.
- Although Imlygic (talimogene laherparepvec) is being studied for the treatment of breast cancer, pancreatic cancer, and SCCHN, there is currently no published evidence supporting its safety or efficacy in this setting. [6]
- The safety and efficacy of Imlygic (talimogene laherparepvec) in combination with other therapies is uncertain and is therefore considered investigational.
    * A randomized, double-blind study evaluated Imlygic (talimogene laherparepvec) as an add-on therapy to Keytruda (pembrolizumab) in patients with unresectable, advanced-stage melanoma. There was no improvement in PFS or OS with Imlygic (talimogene laherparepvec) plus Keytruda (pembrolizumab) relative to Keytruda (pembrolizumab) alone. [7]

Safety [2]

- Safety information is primarily derived from the pivotal OPTiM trial. Median duration of treatment was 23 weeks (range 0.1-78.9 weeks) among patients treated with Imlygic (talimogene laherparepvec).
- The most commonly reported AEs (> 20% incidence) include: flu-like symptoms, fatigue, chills, pyrexia, nausea, injection site pain, and vomiting. An overwhelming majority (90%) of patients treated with Imlygic (talimogene laherparepvec) experienced flu-like symptoms. These reactions were more frequent in the first 3 cycles of treatment and resolved within 3 days of onset.
- Severe AEs included cellulitis, impaired wound healing, and immune-mediated disease (e.g., glomerulonephritis).
- Imlygic (talimogene laherparepvec) is contraindicated in immunocompromised patients, including those with a history of primary or acquired immunodeficient states, leukemia, lymphoma, AIDS, or other clinical manifestations of infection with human immunodeficiency viruses, and those on immunosuppressive therapy, due to the risk of life-threatening disseminated herpetic infection.
- The safety and efficacy of Imlygic (talimogene laherparepvec) has not been studied in patients requiring chronic use of antivirals, systemic corticosteroids at doses of >10 mg prednisone or equivalent, or any medications causing bone marrow suppression.

Cross References
Keytruda, pembrolizumab, Medication Policy Manual, Policy No. dru367
Opdivo, nivolumab, Medication Policy Manual, Policy No. dru390
Opdualag, nivolumab-relatlimab, Medication Policy Manual, Policy No. dru718
Yervoy, ipilimumab, Medication Policy Manual, Policy No. dru238
Mitogen-activated extracellular signal-regulated kinase (MEK) Inhibitors, Medication Policy Manual, Policy No. dru727
BRAF inhibitors, Medication Policy Manual, Policy No. dru728

Codes	Number	Description
HCPCS	J9325	Injection, talimogene laherparepvec (Imlygic), per 1 million plaque forming units

References

1. Andtbacka RH, Kaufman HL, Collichio F, et al. Talimogene Laherparepvec Improves Durable Response Rate in Patients With Advanced Melanoma. *J Clin Oncol.* 2015;33(25):2780-8. PMID: 26014293
2. Imlygic® (talimogene laherparepvec) [package insert]. BioVex, Inc a subsidiary of Amgen Inc; Thousand Oaks, CA; June 2022.
3. Cellular Tissue and Gene Therapies Advisory Committee Meeting to Discuss NDA for talimogene laherparepvec (Imlygic) as a treatment for melanoma. [cited 1/20/2017]. Available from: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/CellularTissueandGeneTherapiesAdvisoryCommittee/UCM444715.pdf.
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5. Dummer R, Gyorki DE, Hyngstrom J, et al. Neoadjuvant talimogene laherparepvec plus surgery versus surgery alone for resectable stage IIIB-IVM1a melanoma: a randomized, open-label, phase 2 trial. Nat Med. United States, 2021:1789-96.
6. National Institutes of Health, Clinicaltrials.gov [website]. [cited periodically]. Available from: www.clinicaltrials.gov.
7. Chesney JA, Ribas A, Long GV, et al. Randomized, Double-Blind, Placebo-Controlled, Global Phase III Trial of Talimogene Laherparepvec Combined With Pembrolizumab for Advanced Melanoma. J Clin Oncol. United States, 2023:528-40.

Revision History

Revision Date	Revision Summary
9/14/2023	No criteria changes with this annual review.
9/23/2022	There were no changes to coverage criteria with this annual review.
10/15/2021	• COT language updated (no change to intent). • No changes to the coverage criteria with this annual review.
10/28/2020	• Continuation of care language was added to the policy. • There were no changes to the intent of the existing coverage criteria.
10/23/2019	No changes to coverage criteria with this annual update.
09/21/2018	No changes to coverage criteria with this annual update.
08/11/2017	No changes to coverage criteria with this annual update.
02/17/2017	Added coverage for stage IV-M1a disease, clarified reauthorization criteria. Moved stage IV-M1b-M1c to investigational from NMN.
02/11/2016	New policy

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Medication Policy Manual **Policy No:** dru463

Topic: Tecentriq, atezolizumab **Date of Origin:** July 15, 2016

Committee Approval Date: September 19, 2024 **Next Review Date:** 2025

Effective Date: January 1, 2025

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Tecentriq (atezolizumab) is an intravenously administered immunotherapy used in the treatment of various cancers. It belongs to a class of medications called programmed death-ligand (PD-L1) blocking antibodies.

Policy/Criteria

Most contracts require pre-authorization approval of Tecentriq (atezolizumab) prior to coverage.

I. Continuation of therapy (COT): Tecentriq (atezolizumab) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 below must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 below must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Tecentriq (atezolizumab) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that one of the following criterion A through E below is met.

A. A diagnosis of **non-small cell lung cancer** (NSCLC) when criterion 1 or 2 below are met:

1. **NSCLC, metastatic (stage IV) disease**, when criteria a and b below are met.

a. One of the following criteria are met (i or ii):

i. There is either no prior use of PD-1 inhibitors or PD-L1 inhibitors (see *Appendix 1*).

OR

ii. Documented prior use of Tecentriq (atezolizumab) with NO progression of disease while on Tecentriq (atezolizumab) adjuvant therapy.

AND

b. Tecentriq (atezolizumab) will be used in one of the following settings (i, ii, or iii):

i. As **monotherapy in the first-line setting** when the tumor has high PD-L1 expression. High PD-L1 expression is defined as PD-L1 stained ≥ 50% of tumor cells [TC ≥ 50%] or PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 10% of the tumor area [IC ≥ 10%]).

OR

ii. As **combination-therapy in the first-line setting** when criteria 1 and 2 below are met:

1. The tumor is an adenocarcinoma (non-squamous).

AND

2. Use is initiated in combination with chemotherapy, such as a platin and taxane.

OR

iii. As **monotherapy in the recurrent setting** when there has been disease progression on or after a platin-containing chemotherapy regimen.

OR

2. **NSCLC, stage II-IIIA disease, as adjuvant therapy,** when all criteria (a through e) below are met.

a. Used in the adjuvant setting, after complete tumor resection.

AND

b. Used as a monotherapy.

AND

c. Documentation of PDL1 expression is provided. PD-L1 expression is defined as PD-L1 stained ≥1% of tumor cells [TC ≥1%]

AND

d. There is clinical documentation of previous adjuvant platinum-containing chemotherapy, unless the patient is ineligible for any platinum-containing chemotherapy (such as cisplatin or carboplatin).

AND

e. There is either no prior use of PD-1 inhibitors or PD-L1 inhibitors (see *Appendix 1*), including but not limited to use of Opdivo (nivolumab) in the neoadjuvant setting.

PLEASE NOTE: Any platinum ineligibility may include poor kidney function, poor performance status (Eastern Cooperative Oncology Group [ECOG] score ≥2), heart failure, other comorbidities, etc.).

OR

B. A diagnosis of **small cell lung cancer** (SCLC), extensive-stage (ES), when criteria 1, 2, and 3 below are met:

1. No prior systemic treatment for extensive-stage SCLC (not including any systemic treatment for early/limited-stage SCLC).

AND

2. Use will be initiated in combination with carboplatin and etoposide.

AND

3. No prior use of PD-1 inhibitors or PD-L1 inhibitors (see *Appendix 1*).

OR

C. A diagnosis of **hepatocellular carcinoma** (HCC), unresectable or metastatic, when criteria 1, 2, and 3 below are met:

1. Patient has a Child-Pugh score of 5 to 6 (class A) [provider attestation].

AND

2. No prior systemic therapy for HCC.

AND

3. No prior use of PD-1 inhibitors or PD-L1 inhibitors (see *Appendix 1*).

OR

D. A diagnosis of **cutaneous melanoma**, unresectable or metastatic, when criteria 1, 2, and 3 below are met:

1. The cancer is BRAF V600 mutation-positive.

AND

2. Tecentriq (atezolizumab) will be administered in combination with Zelboraf (vemurafenib) and Cotellic (cobimetinib).

AND

3. No prior use of PD-1 inhibitors or PD-L1 inhibitors (see *Appendix 1*).

OR

E. A diagnosis of **alveolar soft part sarcoma (ASPS)**, unresectable or metastatic, when criteria 1, 2, and 3 below are met:

1. Prior surgical resection, unless the tumor is unresectable (attestation).

AND

2. Tecentriq (atezolizumab) will be used as a monotherapy.

AND

3. No prior use of PD-1 inhibitors or PD-L1 inhibitors (see *Appendix 1*).

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Tecentriq (atezolizumab) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Tecentriq (atezolizumab) will be authorized in quantities as follows in Table 1 below:

Table 1. QL and Authorization Period

Diagnosis	Dose	Total Coverable Duration of Therapy
Adjuvant NSCLC	Up to a maximum of 420 mg per 7 days (as 840 mg every 14 days, 1200 mg every 21 days, or 1680mg every 28 days)	For 24 weeks, until disease progression, up to 12 months
All other covered diagnoses	Up to a maximum of 420 mg per 7 days (as 840 mg every 14 days, 1200 mg every 21 days, or 1680mg every 28 days)	For 24 weeks, until disease progression

Key: NSCLC: non-small cell lung cancer

C. Reauthorization: Authorization **shall** be reviewed at least every 24 weeks for documented benefit. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met. Specifically, documentation that the medication is providing clinical benefit, including disease stability or improvement, and lack of disease progression, based on an assessment of change in tumor burden. If there is documentation of potential disease progression, a shortened authorization (up to three months) may be approved to allow time for clarification of response to Tecentriq (atezolizumab), including clinical re-evaluation of the patient and reimaging.

PLEASE NOTE: Additional doses of Tecentriq (atezolizumab) will not be authorized without a documented recent assessment by the treating provider (such as oncologist) with objective evidence of response to therapy, such as by re-imaging and use of iRECIST criteria.

IV. Tecentriq (atezolizumab) is considered not medically necessary when used for, EGFR- or ALK-mutated NSCLC as a second-line therapy, after progression on EGFR-or ALK-directed therapy.

V. Tecentriq (atezolizumab) is considered investigational when administered concomitantly with other anti-cancer immuno-, targeted-, and chemotherapies with the exception of those specifically addressed in the coverage criteria above.

VI. Tecentriq (atezolizumab) is considered investigational when used for all other conditions, including but not limited to:

A. Renal cell carcinoma (RCC).

B. Breast cancer (including TNBC and HER-2 positive).

C. Urothelial carcinoma (bladder cancer).

D. Prostate cancer.

E. Ovarian cancer.

F. Soft tissue sarcoma (STS), other than specifically listed above in the coverage criteria.

Position Statement

Summary

- Tecentriq (atezolizumab) is an intravenously (IV) administered programmed death-ligand 1 (PD-L1) blocking antibody (immunotherapy) used in the treatment of several types of cancers.
- The intent of this policy is to cover Tecentriq (atezolizumab) in settings where it has been shown to be safe and effective, as detailed in the coverage criteria, with consideration for other available treatment options.
    * Where there is lack of proven additional benefit and/or lack of demonstrated health outcome (such as overall survival or improved quality of life) relative to alternative therapies, use of Tecentriq (atezolizumab) alone or in combination with other therapies is not coverable ("not medically necessary" or "investigational").
    * It is important to note that the fact that a medication is FDA approved for a specific indication does not, in itself, make the treatment medically reasonable and necessary.
- Many of the clinical indications for immunotherapies (PD-1, PD-L1, and others) have been approved by the FDA and endorsed by clinical guidelines based on surrogate measures such as overall tumor response rate (ORR), disease-free survival (DFS), and progression-free survival (PFS) which are not proven to accurately predict clinically important outcomes such as improved overall survival or improved quality of life.
- *PD-L1 expression testing*: is required for coverage of many clinical indications for PD-1 and PD-L1 inhibitors.
    * There are several ways in which PD-L1 expression can be defined. In addition, how PD-L1 expression is defined varies by tumor type and setting.
    * PD-L1 expression is determined by the FDA-approved companion diagnostic testing, based on both the specific PD-1/PD-L1 inhibitor and the tumor type.
- However, PD-L1 test results are not interchangeable across PD-1/PD-L1 inhibitors and/or indications. There is no conversion available from one type of test to another, such as combined positive score (CPS) versus tumor proportion score (TPS) versus percent of tumor cells (TC). Therefore, the correct test must be conducted for proper selection of patient populations for a given use. National Comprehensive Cancer Network (NCCN) guidelines recommend Tecentriq (atezolizumab) as a potential option in each of the treatment settings listed in the coverage criteria. In general, NCCN recommendations parallel the FDA approved indications.
- The PD-1 and PD-L1 inhibitors have the potential to cause immune-mediated adverse reactions that can result in pneumonitis, colitis, hepatitis, endocrinopathies, and nephritis.

- Tecentriq (atezolizumab) is IV administered as a 1200 mg dose every three weeks. Alternative dosing regimens include 840 mg IV every two weeks or 1680mg IV every four weeks.
- Optimal sequencing of chemotherapy and immunotherapy in many cancers is unknown or the data is evolving. At this time, sequential use of immunotherapies is not supported by current evidence. Specifically, there is no evidence to support the sequential use of different PD-1 or PD-L1 inhibitors once there is disease progression on prior PD-1 or PD-L1 inhibitor therapy, as well as use of adjuvant PD-1/PD-L1 inhibitor after neoadjuvant PD-1/PD-L1 inhibitor therapy (unless explicitly listed in the coverage criteria). Therefore, the use of sequential courses of PD-1/PD-L1 immunotherapy is not coverable.
- There are ongoing studies using Tecentriq (atezolizumab) in a variety of other cancers. However, although initial evidence may be promising, the potential for clinical benefit in these conditions is still being investigated.
- *FDA Indications withdrawn*
    * The FDA indication for urothelial carcinoma (bladder cancer) was withdrawn after a confirmatory trial failed to demonstrate any clinical benefit in this treatment setting. As a result, the coverage of Tecentriq (atezolizumab) for bladder cancer is considered investigational.
    * Locally advanced or metastatic, PD-L1-positive, triple negative breast cancer (TNBC), front-line, in combination with Abraxane (nab-paclitaxel).
    * Confirmatory trials failed to demonstrate any clinical benefit in these treatment settings. As a result, the coverage of Tecentriq (atezolizumab) for these settings is considered investigational.
- *Reauthorization Criteria*: When coverage criteria are met, Tecentriq (atezolizumab) is authorized for six months (24 weeks) of therapy, after which time documentation must be provided to establish that the medication is effective. Specifically, there must be documentation of clinical benefit, including disease stability or improvement and there is a lack of disease progression, based on an assessment of change in tumor burden. Documentation of benefit must include an assessment of the most recent imaging ("restaging scans") and/or re-biopsy by the treating oncologist.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations

are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.

- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

CLINICAL EFFICACY

Non-Small Cell Lung Cancer (NSCLC)

Adjuvant therapy – NSCLC

- Tecentriq (atezolizumab), as a single agent, demonstrated improved disease-free survival (DFS) relative to best supportive care in the adjuvant setting for patients with stage II-IIIA NSCLC after complete tumor resection and standard adjuvant therapy with a platinum-based chemotherapy regimen and, if the tumor is ≥1% PD-L1 positive, defined as PD-L1 stained ≥1% of tumor cells [TC ≥1%]. Patients in the experimental arm received Tecentriq (atezolizumab) every 3 weeks for 16 cycles unless disease recurrence or unacceptable toxicity occurred. [1 2]
    * Patients in the trial received a median of four cycles of adjuvant cisplatin-based chemotherapy after complete resection.
    * Prior use of PD-1/PD-L1 inhibitors was not allowed, such as in the neoadjuvant setting.
    * Although patients with TC >1% PD-L1 expression demonstrated a DFS benefit, patients with a high PD-L1 expression (TC ≥ 50%) appeared to have the most significant DFS benefit based on a pre-determined subgroup analysis.
    * DFS is not a validated endpoint in adjuvant NSCLC and has not been correlated to meaningful clinical outcomes such as overall survival.
- The National Comprehensive Cancer Network (NCCN) NSCLC treatment guideline lists Tecentriq (atezolizumab) as an option in the adjuvant setting for completely resected stage IIB-IIIA or high-risk stage IIA PD-L1 ≥ 1% NSCLC in patients who received previous adjuvant chemotherapy. [3]

Front-line therapy (as monotherapy) - NSCLC:

- The approval of Tecentriq (atezolizumab) as a front-line agent (as monotherapy) for metastatic NSCLC with high PD-L1 expression was based on an open-label (not blinded), phase 3 trial [IMpower110 study] that compared Tecentriq (atezolizumab) with platinum doublet chemotherapy. [2 4]
    * Patients previously treated with PD-1/PD-L1 inhibitors, including in the neoadjuvant, adjuvant, or advanced setting were excluded from inclusion in the trial.
    * The primary endpoint of OS was tested hierarchically according to PD-L1 expression status. Only those in the high PD-L1 expression group (defined as PD-L1 stained ≥ 50% of tumor cells [TC ≥ 50%] or PD-L1 stained tumor-infiltrating

immune cells [IC] covering ≥ 10% of the tumor area [IC ≥ 10%] met the prespecified efficacy boundary.

  * At interim, a seven-month improvement in median OS was reported in the Tecentriq (atezolizumab) arm for patients with high PD-L1 expression.
  * Patients with EGFR or ALK aberrations were enrolled in the trial after progression on ALK/EGFR-directed therapies, but excluded from the primary analysis. In an exploratory analysis, monotherapy with Tecentriq (atezolizumab) was not superior to use of chemotherapy. Therefore, the use of Tecentriq (atezolizumab) for NSCLC after EGFR- or ALK-directed therapy is considered 'not medically necessary' and not coverable.

- Tecentriq (atezolizumab) monotherapy is listed in the NCCN NSCLC guideline as a preferred, recommended therapy among other immunotherapies, for metastatic NSCLC with high PD-L1 (>50%) expression) and no driver mutations. [3]

Front-line therapy, in combination with chemotherapy plus bevacizumab - NSCLC:

- The approval of Tecentriq (atezolizumab) as a front-line therapy for non-squamous metastatic NSCLC was based on a randomized, open-label (not blinded), phase 3 trial
- [IMpower150] that compared atezolizumab (A, Tecentriq)/ carboplatin (C)/ paclitaxel (P)/bevacizumab (B) [ABCP] with BCP alone in patients with metastatic, non-squamous NSCLC. [5]
  * Patients with EGFR or ALK aberrations were excluded from inclusion in the trial.
  * A 4-month survival advantage was reported in the ABCP group relative to the BCP group, with a median OS of 19.2 months, and 7.0 months, respectively [HR 0.71; 95% CI, 0.59, 0.85; p = 0.0002].
  * There were many threats to the reliability of these results, including the lack of blinding and numerous protocol changes during the trial which altered the predetermined efficacy analysis (high potential for bias in the results).
  * Despite the positive OS results, it is not known whether the addition of bevacizumab to Tecentriq (atezolizumab) plus platin-based chemotherapy is superior to Tecentriq (atezolizumab) plus platin-based chemotherapy alone, or whether the additional risks with this multi-drug regimen are acceptable, as ABCP was not formally compared with ACP. However, the median OS for these two groups was numerically similar suggesting a lack of any survival benefit (19.2 months and 19.4 months, respectively). Furthermore, it is not known if the addition of Tecentriq (atezolizumab) to platin-based chemotherapy is superior to platin-based chemotherapy alone. This is an area of ongoing investigation.
  * Additionally, the lack of formal comparison between the ABCP and ACP groups does not allow for an accurate assessment of the potential added safety risks when bevacizumab is added to an immunotherapy-based regimen.
- The NCCN NSCLC treatment guideline lists Keytruda (pembrolizumab)/cisplatin/Alimta (pemetrexed) as a preferred category 1 recommendation for front-line use in metastatic, non-squamous NSCLC. Tecentriq (atezolizumab)/carboplatin/paclitaxel/bevacizumab is listed as an 'other' category 1 recommendation. [3]

Front-line therapy, in combination with a platinum plus a taxane – NSCLC:

- Tecentriq (atezolizumab) was also approved as part of a front-line regimen for non-squamous metastatic NSCLC based on a randomized, open-label (not blinded), phase 3 trial that compared Tecentriq (atezolizumab) plus nab-paclitaxel and carboplatin with nab-paclitaxel and carboplatin with or without pemetrexed switch maintenance. [6]
    * Most patients had no EGFR or ALK aberrations.
    * Tecentriq (atezolizumab) was initiated with chemotherapy (carboplatin and nab-paclitaxel) as induction and then continued as monotherapy versus carboplatin plus nab-paclitaxel induction followed by pemetrexed switch maintenance or best supportive care (BSC).
    * The Tecentriq (atezolizumab) treatment arm demonstrated improved overall survival relative to the chemotherapy arm, with a 4.7-month improvement in median OS and 1.5-month improvement in median PFS.
    * It was noted that the combination of Tecentriq (atezolizumab) with chemotherapy may add additional toxicity relative to either therapy alone.
    * Applicability of the results to patients with squamous histology or patients with EGFR or ALK genetic aberrations cannot be determined as the sample size for these groups was too small.
    * The NCCN NSCLC treatment guideline lists Tecentriq (atezolizumab) plus carboplatin and nab-paclitaxel in the first-line, non-squamous, metastatic NSCLC setting as one of several 'other recommended' therapy options. [3]

Subsequent-line therapy (after disease progression on platinum-based front-line therapy) - NSCLC:

- Tecentriq (atezolizumab), as a single agent, demonstrated improved OS relative to docetaxel in patients with locally advanced or metastatic NSCLC who had disease progression after standard therapy with a platinum-based chemotherapy regimen and, if the tumor was EGFR- or ALK-positive, an appropriate tyrosine kinase inhibitor. [7 8]
    * A three- to four-month improvement in median overall survival was demonstrated with Tecentriq (atezolizumab) relative to docetaxel. Benefit was noted regardless of PD-L1 expression.
    * Prior treatment with PD-1/PD-L1 inhibitors was not allowed.
- The National Comprehensive Cancer Network (NCCN) NSCLC treatment guideline lists Tecentriq (atezolizumab), Opdivo (nivolumab), and Keytruda (pembrolizumab) among preferred category 1 recommendations for locally advanced or metastatic NSCLC that progressed on or after standard front-line therapy when there has been no prior use of anti-PD-1/PD-L1 therapy. [3]

Small Cell Lung Cancer (SCLC)

- The initial approval in SCLC was based on the results of a phase 3 RCT [IMpower133] that compared Tecentriq (atezolizumab) plus chemotherapy (carboplatin plus etoposide) with chemotherapy alone (placebo arm) in patients with untreated, extensive-stage SCLC (ES-SCLC). There was a small, but statistically significant difference in the 1-year survival rate that favored patients in the Tecentriq (atezolizumab) treatment arm. [2 9]

    * Subjects included in the study had no prior treatment for extensive-stage SCLC. If they had prior treatment for limited-stage SCLC, they had to have been treated with curative intent and must have had a treatment-free interval of at least 6 months since their last chemotherapy, radiotherapy, or chemoradiotherapy.
    * Patients with untreated or symptomatic CNS metastasis were not included in the study.
    * Tecentriq (atezolizumab) was initiated with carboplatin plus etoposide (given for four cycles) and was then continued as maintenance until disease progression.
    * Overall survival at 12 months was 51.7% and 38.2% in the Tecentriq (atezolizumab) and placebo arms, respectively [HR 0.70; 95% CI: 0.54, 0.91; p = 0.007]. Median OS was 12.3 months [95% CI: 10.8, 15.9] and 10.3 months [95% CI: 9.3, 11.3], respectively. No p-value was reported for the medians. Because the confidence intervals overlap, the meaningfulness of these findings is difficult to interpret.
- The NCCN SCLC guidelines include front-line use of Tecentriq (atezolizumab) as a preferred treatment option as initial therapy for ES- SCLC based on this data. [3]
- Optimal sequencing of chemotherapy and immunotherapy in SCLC has not been studied. Sequential use of immunotherapies is not supported by current evidence.
- Other Neuroendocrine Tumors: Neuroendocrine tumors include a variety of tumor types, such as GI tract bronchopulmonary (including SCLC), thymic, and pancreatic, among others. [10] Although SCLC is classified as a neuroendocrine tumor. Tecentriq (atezolizumab) is coverable only for neuroendocrine that is "managed as SCLC" per guidelines or trial evidence. There is insufficient evidence at this time to conclude safety or efficacy of Tecentriq (atezolizumab) for any other type of neuroendocrine tumor, aside from SCLC.

Hepatocellular carcinoma (HCC)

- The initial approval in HCC was based on the results of one open-label, phase 3 RCT [IMbrave150] in patients with previously untreated, unresectable, or metastatic HCC. [2 11]
    * The trial compared Tecentriq (atezolizumab) given in combination with bevacizumab with Nexavar (sorafenib) as a monotherapy.
    * All patients included in the study had Child-Pugh (CP) class A disease. The trial excluded sicker patients (Class B and C; see Appendix 2).
    * An early analysis of overall survival (OS) favored Tecentriq (atezolizumab) plus bevacizumab over Nexavar (sorafenib),With median OS reached in the Nexavar (sorafenib) arm at 13.2 months but not been reached in the Tecentriq (atezolizumab) plus bevacizumab combination arm at 17 months.
    * Subsequently, an updated analysis after 12 additional months reported median OS of 19.2 months with Tecentriq (atezolizumab) plus bevacizumab and 13.4 months with Nexavar (sorafenib). [12]
    * It is unknown how Tecentriq (atezolizumab) plus bevacizumab compares to either agent alone in this setting. In addition, the safety and efficacy of Tecentriq (atezolizumab) in combination with medications other than noted above is

unknown. A phase 3 trial of Tecentriq (atezolizumab) in combination with Cometriq (cabozantinib) was non-inferior to Nexavar (sorafenib) monotherapy. [13]

- The NCCN guidelines include the front-line use of Tecentriq (atezolizumab) plus bevacizumab among treatment options as an initial systemic therapy for advanced HCC. [3]
- Various rating scales may be used to estimate degree of hepatic dysfunction with chronic liver disease. In the IMbrave150 trial for HCC, the Child-Pugh (CP) score for cirrhosis mortality was used to screen for HCC patients with less severe liver disease. The CP score is an estimate of chronic liver disease and cirrhosis and is used as a prognostic indicator. Points are assigned for markers of hepatic dysfunction, including liver function tests, ascites, and encephalopathy. CP score is reported as a range, given it is an estimation assigned by the treating provider. Based on score, a CP class is assigned. The lower end of the reported range may be used as a marker for illness/prognosis (e.g., CP A6/B7 meets intent of coverage criteria of class A) (see Appendix 2).

Cutaneous Melanoma, BRAF mutation-positive

- The approval of Tecentriq (atezolizumab) in BRAF mutation-positive cutaneous melanoma is based on a large, double-blind, placebo-controlled RCT [IMspire150 study] that compared Tecentriq (atezolizumab) plus Zelboraf (vemurafenib) plus Cotellic (cobimetinib) with placebo plus Zelboraf (vemurafenib) plus Cotellic (cobimetinib). [2 14]
  * Subjects in the study had unresectable stage IIIC or stage IV (metastatic) cutaneous melanoma with a BRAF V600 mutation.
  * All patients were naïve to prior systemic therapy in the metastatic disease setting.
  * There was a PFS advantage of approximately four and a half months in the Tecentriq (atezolizumab) versus the placebo treatment arm [15.1 months and 10.6 months, respectively]. These results were statistically significant; however, the clinical meaningfulness of this difference is not known.
  * The OS data in this trial are not yet mature. No statistical difference in survival between the two therapy arms has been detected to date.
- Due to the design of this study and the current lack of proven clinical benefit, it is not known if adding Tecentriq (atezolizumab) to front-line BRAF inhibitors is superior to waiting to use anti-PD-1/PD-L1 therapies in the subsequent-line setting in BRAF mutation-positive melanoma. This should be considered in the decision when choosing a front-line therapy as sequential use of anti-PD-1/PD-L1 therapies is not covered by the health plan.
- The NCCN cutaneous melanoma guideline includes the use of Tecentriq (atezolizumab) in combination with Zelboraf (vemurafenib) and Cotellic (cobimetinib) among recommended options for the front-line treatment of BRAF mutation-positive metastatic or unresectable melanoma. [3]

Alveolar soft part sarcoma (ASPS)

- Alveolar soft part sarcoma (ASPS) is a very rare type of soft tissue sarcoma (STS) (less than 1% of all STS).

- The approval of Tecentriq (atezolizumab) in advanced ASPS is based one unpublished, non-randomized, multicenter, single-arm phase 2 trial in 49 patients with ASPS not curable by surgery (ML39345). [2 15]
    * All enrolled patients had prior surgery and were stage IV at the time of diagnosis.
    * A majority had prior other treatments (55% more than one), including radiation therapy (55%), chemotherapy (53%).
    * The primary outcome was overall response rate (ORR) (24%). Twelve patients (24%) had a partial response, and none had a complete response.
- The NCCN soft tissue sarcoma guideline includes the use of Tecentriq (atezolizumab) among preferred recommended options for unresectable or metastatic ASPS. [3]

REAUTHORIZATION

- When coverage criteria are met, Tecentriq (atezolizumab) is authorized for six months (24 weeks) of therapy, after which time documentation must be provided to establish that the medication is effective. Specifically, there must be documentation of clinical benefit, including disease stability or improvement and there is a lack of disease progression, based on an assessment of change in tumor burden.
    * The standard of care for evaluation of response to cancer immunotherapy, such as Tecentriq (atezolizumab), is use of the iRECIST criteria for assessment of tumor burden. [16]
    * The iRECIST criteria include use of quantitative and qualitative criteria for assessment of change in tumor burden for target lesions and non-target lesions. [17]
        - Quantitative measurements for target lesions (tumor size and % change)
        - Qualitative evaluation for non-target lesions (present/disappeared/ unequivocal progression)
    * Documentation of benefit must include an assessment of the most recent imaging ("restaging scans") by the treating oncologist. Given the complexity of the evaluation, including use of the iRECIST criteria, Tecentriq (atezolizumab) will not be reauthorized without an assessment of response to therapy, such a partial response (iPR), complete response (iCR), or stable disease (iSD).
    * Use of immunotherapy may result in pseudoprogression, due to immune and T-cell activation, which can appear similar to tumor flare. If there is documentation of potential disease progression ["unconfirmed progressive disease (iUPD)"], a shortened authorization (up to three months) may be approved to allow time for clarification of response to Tecentriq (atezolizumab), including clinical re-evaluation of the patient and reimaging. Guidelines recommend reimaging for iUPD after 4-8 weeks.
    * If a patient has confirmed, unequivocal new lesions (progression of disease, iPD), additional Tecentriq (atezolizumab) is not coverable. If a new lesion is equivocal, iUPD reassessment by the treating oncologist with repeat imaging would apply (as noted above).

NON-COVERED USES

Triple Negative Breast Cancer (TNBC)

- Trials of Tecentriq (atezolizumab) in TNBC have demonstrated variable results such that the benefit of Tecentriq (atezolizumab) in TNBC remain uncertain at this time.
- Front-line advanced [locally advanced (unresectable) or metastatic] treatment setting:
  * The FDA indication for use as a front-line therapy for locally advanced or metastatic, PD-L1-positive, triple negative breast cancer (TNBC) when used in combination with Abraxane (nab-paclitaxel) was withdrawn after a confirmatory trial failed to demonstrate any clinical benefit in this treatment setting. As a result, the coverage of Tecentriq (atezolizumab) for TNBC is considered investigational.
  * The rationale is as follows:
    - Tecentriq (atezolizumab) in combination with Abraxane (nab-paclitaxel) is FDA approved as a first-line therapy for locally advanced (unresectable) or metastatic TNBC (mTNBC) when the tumor expresses PD-L1.
    - However, this combination regimen has not adequately been demonstrated to provide any additional benefit, or to have an acceptable safety profile over, other coverable treatment options. The confirmatory trial failed to demonstrate any clinical benefit in this treatment setting. As a result, the coverage of Tecentriq (atezolizumab) for TNBC is considered investigational.
    - Accelerated FDA approval was granted based on an exploratory analysis, which found a small improvement in progression-free survival (PFS) in patients with tumors that express PD-L1; however, no difference in overall survival, or any other clinically relevant outcome, was demonstrated. [2 18]
    - As is the case with medications approved via the FDA accelerated process, further studies are required to show that the medication improves a clinically relevant outcome, such as improved survival or quality of life, before regular (continued) approval is granted.
    - While post-hoc subgroup analyses suggested a potential benefit in the PD-L1 positive population, this result was not statistically significant by the predefined endpoints in the trial (using *a priori* study criteria). [18 19]
    - There is a known potential for toxicity with PDL-1 inhibitors, including Tecentriq (atezolizumab).
    - In summary, given a modest improvement in a surrogate endpoint (PFS), a failure in the confirmatory trial to find an improvement in health outcomes (no proven overall survival benefit), conflicting data from other trials in this setting, risk of harms with PD-L1 inhibitors, and the availability of several other treatment options, the use of Tecentriq (atezolizumab) for front-line treatment mTNBC is considered investigational.

* The study upon which the accelerated FDA approval for advanced TNBC was based [IMpassion130 study] compared front-line use of Tecentriq (atezolizumab) plus Abraxane (nab-paclitaxel) versus Abraxane (nab-paclitaxel) alone in patients with unresectable locally advanced, or metastatic TNBC. Subjects were enrolled, regardless of PD-L1 expression. [2 18]
    - Accelerated approval was granted based on an improvement in PFS in the combination arm relative to the Abraxane (nab-paclitaxel) alone (placebo) arm. The initial primary endpoint was PFS in the intent-to-treat population. The primary endpoint was later modified to evaluate the PD-L1-positive population.
    - The median PFS was 7.5 months and 5.0 months (HR 0.62 [95% CI: 0.49, 0.78]; p<0.001), respectively in the PD-L1 positive cohort (PD-L1 [IC] ≥ 1%).
    - The trial was not able to demonstrate improvement in median OS or any other clinically relevant outcome, such as symptom control or quality of life. As with all medications approved via the FDA accelerated pathway, continued approval is contingent on additional trials that demonstrate clinical benefit.
    - Updated results from the second interim analysis again reported no statistically significant improvement in OS in the pre-specified ITT population. The significance of the OS difference in the PD-L1 positive cohort is unknown, as statistical testing was not possible for this exploratory analysis. [19]
    - Overall, there was a small increase in grade 3 and 4 adverse effects when Tecentriq (atezolizumab) was added to Abraxane (nab-paclitaxel). Additionally, immune reactions requiring systemic corticosteroids occurred in 13% of subjects in the Tecentriq (atezolizumab) arm.
* In addition to the use of a non-validated surrogate endpoint with unknown clinical relevance, there were several potential sources of bias in the trial that may overstate potential for benefit including a higher rate of Abraxane (nab-paclitaxel) discontinuation from the placebo arm for reasons other than meeting a study endpoint.
* Subsequently, other trials of Tecentriq (atezolizumab) have demonstrated variable results such that the benefit of Tecentriq (atezolizumab) in first-line treatment of unresectable TNBC remain uncertain ('investigational') at this time.
    - The FDA issued a safety warning after OS reportedly favored placebo plus paclitaxel over Tecentriq (atezolizumab) plus paclitaxel in the first-line treatment of locally advanced/metastatic setting in the IMpassion-131 trial. [20]
    - Further data in the metastatic setting from the IMpassion-132 trial has been delayed after a major expansion in the population was announced. [21]
* The NCCN breast cancer guideline removed Tecentriq (atezolizumab). [3]

- Neoadjuvant TNBC:
    * The IMpassion-031 trial found an improvement in of pathological complete response (cPR) rates, the co-primary endpoint, associated with the addition of Tecentriq (atezolizumab) to neoadjuvant chemotherapy [Abraxane (nab-paclitaxel)] as compared to use of Abraxane (nab-paclitaxel) alone in patients with early TNBC (58% vs. 41%, respectively). [22]
    * Subsequently, the NeoTRIPaPDL1 trial found no difference in the secondary pathological complete response (cPR) associated with the addition of Tecentriq (atezolizumab) to neoadjuvant chemotherapy [carboplatin/Abraxane (nab-paclitaxel)] versus chemotherapy alone. [23]

Other breast cancer:

- One Phase 3 trial found no benefit with the addition of Tecentriq (atezolizumab) to neoadjuvant chemotherapy for HER2-positive BC (Impassion050). [24]
- Currently, there is insufficient evidence for the use of Tecentriq (atezolizumab) for breast cancer in all other BC settings, including adjuvant, and subsequent therapy (second-line or beyond) settings for breast cancer (TNBC or other).

Hepatocellular Carcinoma, Adjuvant Use

- A phase 3, open-label RCT [IMbrave050] evaluating Tecentriq (atezolizumab) in combination with bevacizumab as an adjuvant therapy (after surgical resection) in patients with high-risk, resectable hepatocellular carcinoma improved recurrence-free survival (RFS) relative to active surveillance; however, there are currently no mature outcomes data available. This is not an FDA-approved use for Tecentriq (atezolizumab). [25]

Other Investigational Uses

- Urothelial Carcinoma (UC, Bladder cancer):
    * Tecentriq (atezolizumab) initially received Accelerated approval as a subsequent therapy (after disease progression on a cisplatin-based chemotherapy regimen) for unresectable or metastatic bladder cancer based on tumor response rate in a non-comparative (single-arm), observational study [IMvigor-210 study]. [26]
    * A subsequent phase 3 trial [IMvigor-211 study] intended to confirm the efficacy of Tecentriq (atezolizumab) in the bladder cancer setting failed to demonstrate an OS advantage over standard chemotherapy in the second-line setting. [27] Based on this failed confirmatory trial the manufacturer voluntarily withdrew the bladder cancer indication. Because there is no proven net health benefit relative to the standard of care, the use of Tecentriq (atezolizumab) for bladder cancer is considered investigational.
    * An additional follow-on, phase 3 trial of Tecentriq (atezolizumab) in the adjuvant muscle-invasive bladder cancer (MIBC) setting failed to meet its primary end-point (disease-free survival) versus best supportive care [IMvigor-010 study]. [28]
- Renal Cell Carcinoma (RCC):
    * A phase 3 study [IMmotion 151] of Tecentriq (atezolizumab) plus bevacizumab versus Sutent (sunitinib) in patients with clear cell or sarcomatoid, metastatic renal cell carcinoma (RCC) reported a PFS advantage for the combination

therapy treatment arm in patients with PD-L1-positive tumors (PD-L1 ≥ 1%). [29] However, there was no OS benefit seen at the final analysis. [30]

* A phase 3 trial of adjuvant Tecentriq (atezolizumab) for high-risk RCC failed to meet the prespecified endpoints. [31]
* Tecentriq (atezolizumab) was studied in combination with Cabometyx (cabozantinib) in patients with advanced RCC who had progressed after immune checkpoint inhibitor therapy [CONTACT-03]. The addition of Tecentriq (atezolizumab) to Cabometyx (cabozantinib) did not improve clinical outcomes and led to increased toxicity versus Cabometyx (cabozantinib) alone.[32]

- **Other phase 3 trials that did not demonstrate a clinical benefit**: [31-34]
  * Tecentriq (atezolizumab) failed to meet its prespecified endpoints in several additional studies including colorectal cancer [IMblaze-370], ovarian cancer [IMagyn050], and prostate cancer [IMbassador250].
  * A phase 3, open-label RCT [IPSOS] evaluating Tecentriq (atezolizumab) as a front-line therapy in patients with stage IIIB or IV NSCLC who were deemed unsuitable to receive standard platinum-based chemotherapy due to an ECOG PS of 2 to 3 demonstrated an improvement in OS relative to single-agent chemotherapy. Though the OS difference was statistically significant it was not clinically relevant (median OS improvement of 1 month).[33]Multiple trials are ongoing in various soft tissue sarcomas (STS) (other than ASPS).

Dosing and Administration [2]

- Tecentriq (atezolizumab) is dosed as 1200 mg intravenously (IV) every 21 days.
- Alternative dosing regimens include 840 mg IV every two weeks or 1680 mg IV every four weeks until disease progression or unacceptable toxicity.
- Adjuvant therapy, such as for NSCLC, is limited to a finite course (as detailed in the Quantity Limits), which is in line with FDA prescribing information.

Appendix 1: FDA-approved PD-1 and PD-L1 blocking monoclonal antibody therapies [a]
Programmed death receptor-1 (PD-1) inhibitors
Jemperli (dostarlimab)
Keytruda (pembrolizumab)
Libtayo (cemiplimab-rwlc)
Loqtorzi (toripalimab)
Opdivo (nivolumab)
Tevimbra (tislelizumab)
Zynyz (retifanlimab-dlwr)
Programmed death-ligand 1 (PD-L1) inhibitor
Bavencio (avelumab)
Imfinzi (durvalumab)
Tecentriq (atezolizumab)

[a] Or as listed on the FDA.gov website

Appendix 2: Child Pugh (CP) Score [a]	
Points	***Class***
5-6	Class A
7-9	Class B
10-15	Class C

[a] CP is reported as a range, given it is an estimation of chronic liver disease. The lower end of the reported range may be used as a marker for illness/prognosis (example: a CP score of A6/B7 meets intent of coverage criteria of "class A"). However, CP scoring was developed for use in determining surgical risk and not specifically as a marker for cancer.

Cross References
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Abraxane, nab-paclitaxel (a.k.a. albumin bound paclitaxel, paclitaxel albumin-stabilized nanoparticle formulation, ABI-007), Medication Policy Manual, Policy No. dru310
Bavencio, avelumab, Medication Policy Manual, Policy No. dru499
BRAF inhibitors, Medication Policy Manual, Policy No. dru728
Imfinzi, durvalumab, Medication Policy Manual, Policy No. dru500
Jemperli, dostarlimab, Medication Policy Manual, Policy No. dru673
Keytruda, pembrolizumab, Medication Policy Manual, Policy No. dru367
Libtayo, cemiplimab, Medication Policy Manual, Policy No. dru565
Mitogen-activate extracellular signal-regulated kinase (MEK) Inhibitors, Medication Policy Manual, Policy No. dru727
Opdivo, nivolumab, Medication Policy Manual, Policy No. dru390

Codes	Number	Description
HCPCS	J9022	Injection, atezolizumab (Tecentriq), 10 mg

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Revision History

Revision Date	Revision Summary
9/19/2024	**Effective 1/1/2025:** Change reauthorization from 'may' to 'shall.' Operationally, all approvals will be for 24 weeks (6 months). Ongoing therapy (beyond 24 weeks) will be subject to reauthorization review every 24 weeks, for documentation of disease stability or improvement and lack of disease progression.
12/7/2023	No criteria changes with this annual review.
6/15/2023	Added coverage criteria for advanced alveolar soft part sarcoma (ASPS) (effective 7/15/2023).
12/9/2022	• Clarified wording of criteria for operational consistency (PD-L1 expression; provider attestation for Child-Pugh score, Quantity Limit table). • Clarify for adjuvant NSCLC criteria "no prior use of PD-1/PD-L1 inhibitors", given the recent approval of Opdivo (nivolumab) for NSCLC neoadjuvant use. • Added prostate, ovarian, and HER-2 positive breast cancer to the list of "investigational uses."
3/18/2022	• Coverage criteria for use in the adjuvant setting in NSCLC was added to align with label. • Clarified that one of the following is required for use of Tecentriq (atezolizumab) in metastatic NSCLC: no prior use of PD-1/PD-L1 or no progression on prior Tecentriq (atezolizumab) treatment.
10/15/2021	The coverage position for triple negative breast cancer (TNBC) was changed from 'not medically necessary' to 'investigational' with this update. The confirmatory clinical trial failed to demonstrate any clinical benefit in this population, so the manufacturer voluntarily withdrew this indication (it is no longer part of FDA labeling).

Revision Date	Revision Summary
4/21/2021	• The coverage criteria in urothelial carcinoma (bladder cancer) were removed with this update. Coverage in this population was moved to the 'investigational' section of the policy. The confirmatory clinical trial failed to demonstrate any clinical benefit in this population so the manufacturer voluntarily withdrew this indication (it is no longer part of FDA labeling). • Streamlined coverage under **NSCLC** by removing the criterion requiring confirmation that no EGFR or ALK genomic aberrations are present *(this is a well-observed standard of care).* • Streamlined coverage under **SCLC** by removing the criterion asking for details on prior treatment in limited-stage disease and the criterion surrounding the steroid requirement in CNS metastasis. • Added a criterion under **HCC** stating there has been no prior use of PD-1/ PD-L1 inhibitors to be consistent with other policy sections. • Added criteria for BRAF-positive **cutaneous melanoma** when used in combination with vemurafenib and cobimetinib. • Clarified the language under investigational section related to concomitant therapies by adding use with 'targeted therapies' (in addition to immuno- and chemotherapies) other than those specifically addressed in the policy as investigational. *(no change to original intent)* • Clarified the language surround NMN vs Investigational uses of atezolizumab in **TNBC** *(no change to original intent).*
10/28/2020	• Simplified coverage criteria for bladder cancer. • Added coverage criteria for several newly FDA-approved indications: - Hepatocellular carcinoma - As monotherapy in the first-line setting for non-small cell lung cancer (NSCLC) for high PD-L1 expressing tumors. - As combination therapy in the first-line setting for nonsquamous NSCLC when used with chemotherapy, such as a taxane and platin.
6/15/2020	Removed references to brand Avastin from policy to account for upcoming changes in biosimilars policy (dru620).
1/22/2020	Added continuation of therapy (COT) criteria (no change to intent of coverage criteria).
7/24/2019	Effective 8/15/2019: • Added use in triple negative breast cancer (TNBC), first-line, a new indication approved via the FDA accelerated approval pathway, as not medically necessary. • Updated dosing, to include alternative dosing intervals every two or four weeks.
4/25/2019	Add the concomitant use of bevacizumab with Tecentriq (atezolizumab) plus chemotherapy for NSCLC to "Not Medically Necessary" indications, based on the low quality of the evidence and the availability other similar therapies.

Revision Date	Revision Summary
1/31/2019	Added coverage criteria for extensive-stage SCLC.
7/20/2018	Updated criteria under urothelial carcinoma to clarify coverage in the front-line setting for cisplatin-ineligible patients only when PD-L1 expressing and any platinum-ineligible patients, regardless of PD-L1 expression.
4/20/2018	No changes to coverage criteria with this annual update. Clarified authorization is valid "until disease progression" (no change to intent).
9/8/2017	• Updated criteria under urothelial carcinoma to include coverage as front-line for cisplatin ineligible patients. • Added criteria for coverage as a subsequent therapy for metastatic NSCLC.
7/15/2016	New policy.

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Medication Policy Manual

Policy No: dru479

Topic: Ocrevus, ocrelizumab

Date of Origin: December 16, 2016

Committee Approval Date: December 9, 2022

Next Review Date: December 2023

Effective Date: March 1, 2023

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Ocrevus (ocrelizumab) is an intravenously administered medication indicated for the treatment of relapsing or primary progressive forms of multiple sclerosis. It works by destroying certain immune cells that are involved in the multiple sclerosis immune response.

Policy/Criteria

Most contracts require pre-authorization approval of Ocrevus (ocrelizumab) prior to coverage.

I. Continuation of therapy (COT): Ocrevus (ocrelizumab) may be considered medically necessary for COT when full policy criteria below are met.

II. New starts (treatment-naïve patients): Ocrevus (ocrelizumab) may be considered medically necessary when Site of Care administration requirements are met [refer to Medication Policy Manual, Site of Care Review, dru408].

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Ocrevus (ocrelizumab) coverable only under the medical benefit (as a provider-administered medication).

B. Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

Position Statement

Summary

- Ocrevus (ocrelizumab) is a monoclonal antibody used as monotherapy for the treatment of patients with primary progressive multiple sclerosis (PPMS) and relapsing forms of multiple sclerosis (MS).
- Ocrevus (ocrelizumab) is considered a disease-modifying multiple sclerosis treatment. Other disease-modifying multiple sclerosis treatments for relapsing forms of MS include Lemtrada (alemtuzumab), interferon beta products (Avonex, Rebif, Betaseron, Extavia, or Plegridy), fingolimod (generic, Gilenya, Tascenso ODT), glatiramer acetate, Aubagio (teriflunomide), and dimethyl fumarate. Rituximab may also be used off label for the treatment of relapsing forms of MS. [1]
- Ocrevus (ocrelizumab) has not been studied in combination with other disease-modifying MS medications and it is therefore not recommended that Ocrevus (ocrelizumab) be administered concomitantly with other disease-modifying MS medications as efficacy and safety have not been established. Concomitant use of Ocrevus (ocrelizumab) with any other disease-modifying therapy for MS is considered investigational.
- Ocrevus (ocrelizumab) is an intravenously infused medication. The starting dose is 300 mg given on day one followed by 300 mg two weeks later. Thereafter, Ocrevus (ocrelizumab) is given every 6 months at a dose of 600 mg.
- The safety and effectiveness of Ocrevus (ocrelizumab) in conditions other than PPMS or relapsing forms of MS have not been established.

Clinical Efficacy in Multiple Sclerosis

- Ocrevus (ocrelizumab) has been shown to reduce elapse rate, slows disability progression, and slows worsening of disease based on MRI outcomes in patients with relapsing forms of MS. [2]
    * Two identical, 96-week studies (OPERA I and OPERA II), evaluated the effects of Ocrevus (ocrelizumab) compared to Rebif (interferon beta-1a) in patients with relapsing forms of MS. Ocrevus (ocrelizumab) was superior to interferon beta-1a in reducing annualized relapse and in slowing confirmed disability progression. On MRI, the patients in the Ocrevus (ocrelizumab) group had fewer new and/or enlarging T2 lesions, less T1 lesions, and a reduced rate of total brain volume loss relative to the Rebif (interferon beta-1a) group.
- Ocrevus (ocrelizumab) has been shown to slow disability progression, and slow the worsening of MRI outcomes in patients with PPMS. [3]
    * One 120-week study (ORATORIO), evaluated the effects of Ocrevus (ocrelizumab) relative to placebo in patients with PPMS. Ocrevus (ocrelizumab) was superior to placebo reducing the proportion of patients who had sustained 12-week confirmed disability progression. The treatment group also showed a significant decrease in T2 volume and showed significantly less brain volume loss on MRI.

Safety [4]

- Ocrevus (ocrelizumab) contains warnings for infusion reactions, infections, and risk of malignancy.
- Common adverse events include upper respiratory tract infections, infusion reactions, skin infections, and lower respiratory tract infections.

Dosing and Administration [4]

- Ocrevus (ocrelizumab) is administered as an intravenous (IV) infusion.
- The starting dose is 300 mg IV followed by 300 mg IV two weeks later. Subsequent doses of Ocrevus (ocrelizumab) are then given every 6 months at a dose of 600 mg IV as a single infusion.

Ocrevus (ocrelizumab) – Use in Other Conditions

- Due to a lack of published data, the use of Ocrevus (ocrelizumab) in conditions other than relapsing forms of MS and PPMS is considered investigational.
- While Ocrevus (ocrelizumab) has a similar mechanism of action to rituximab, it has not been studied for the same indications. Thus, due to a lack of data, these conditions are considered investigational.

Neuromyelitis Optica Spectrum Disorders (NMOSD)

- Neuromyelitis optica spectrum disorders (NMOSD; previously known as Devic disease) are characterized by a combination of bilateral optic neuropathy and cervical myelopathy. While both NMOSD and MS are demyelinating diseases they are considered different diseases based on unique immunologic features and differences in imaging features, biomarkers, and neuropathology. [5]

- For acute attacks and relapses of NMOSD, treatment usually consists of intravenous glucocorticoids followed soon by plasmapheresis for refractory or progressive symptoms. For prevention of attacks, systemic immunosuppression with agents including azathioprine, mycophenolate mofetil, rituximab, and mitoxantrone has been used, given the evidence that humoral autoimmunity plays a role in the pathogenesis of NMO. [6,7]
- Rituximab has been shown to the frequency of NMOSD relapses and neurologic disability based on results from one systematic review. However, the optimal treatment regimen and duration have not been determined and additional long-term safety experience is needed to clarify the role of rituximab as a first-line option. [8]
- There is no published evidence to support the use of Ocrevus (ocrelizumab) for NMOSD.

Appendix A: Disease-Modifying Agents Used in the Treatment of Multiple Sclerosis (MS)
Aubagio (teriflunomide)
Bafiertam (monomethyl fumarate)
Dimethyl fumarate
Fingolimod (generic, Gilenya, Tascenso ODT)
Glatiramer acetate
Interferon beta-1a (Avonex, Rebif)
Interferon beta-1b (Betaseron, Extavia)
Kesimpta (ofatumumab)
Lemtrada (alemtuzumab)
Mavenclad (cladribine)
Mayzent (siponimod)
Novantrone (mitoxantrone)
Ocrevus (ocrelizumab)
Plegridy (peginterferon beta-1a)
Ponvory (Ponesimod)
Rituximab[1]
Tysabri (natalizumab)
Vumerity (diroximel fumarate)
Zeposia (ozanimod)

[1] Rituximab is not FDA-approved for use in MS, but has evidence for efficacy.

Cross References
Site of Care Review, Medication Policy Manual, Policy No. dru408
Non-preferred glatiramer products, Medication Policy Manual, Policy No. dru570
Non-preferred multiple sclerosis treatments, Medication Policy Manual, Policy No. dru511
Tysabri, natalizumab, Medication Policy Manual, Policy No. dru111

Codes	Number	Description
HCPCS	J2350	Injection, ocrelizumab (Ocrevus), 1 mg
ICD-10	G35	Multiple sclerosis

References

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Revision History

Revision Date	Revision Summary
12/9/2022	Updated Appendix A.
10/15/2021	• Removed clinical coverage criteria (effective 1/1/2022). • Updated Appendix A.
1/20/2021	• Clarified quantity limits. • Updated Preferred Disease-Modifying Therapies (DMTs).
1/22/2020	• Added continuation of therapy (COT) criteria (no change to intent of coverage criteria). • Revised step therapy requirements to include Mavenclad (cladribine). • Revised definition of relapsing form of MS.
1/31/2019	Clarified re-authorization requirements.
5/18/2018	Added Ocrevus (ocrelizumab) to the site of care program, effective 9/1/2018.
3/19/2018	Revised step therapy requirements to include Aubagio (teriflunomide).
1/19/2018	Clarified authorization periods. No change to intent of covered doses.
8/11/2017	• Revised step therapy requirements and definition of "ineffectiveness." • Added criteria for aggressive disease. • Removed Ocrevus (ocrelizumab) from site of care program.
4/14/2017	Updated indication, dosing, and administration based on prescribing information.
12/16/2016	New Policy effective upon FDA approval of Ocrevus (ocrelizumab).

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Medication Policy Manual

Policy No: dru480

Topic: Exondys 51, eteplirsen

Date of Origin: January 13, 2017

Committee Approval Date: June 20, 2024

Next Review Date: 2024

Effective Date: October 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Exondys 51 (eteplirsen) is an intravenous medication that may be used for Duchenne muscular dystrophy (DMD) when patients have a specific gene mutation. A clinical benefit, such as improved ambulation, of Exondys 51 (eteplirsen) has not been established.

Policy/Criteria

Most contracts require pre-authorization approval of Exondys 51 (eteplirsen) prior to coverage.

I. Continuation of therapy (COT): Exondys 51 (eteplirsen) is considered investigational for all conditions, per the full policy criteria below.

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Exondys 51 (eteplirsen) is considered investigational for all conditions, including Duchenne muscular dystrophy (DMD) that is amenable to exon 51 skipping (Table 1). However, if found to be medically necessary, criteria A must also be met:

A. Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, Site of Care Review, dru408].

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Exondys 51 (eteplirsen) coverable under the medical benefit (as a provider administered medication).

B. Although the use of Exondys 51 (eteplirsen) is considered investigational for all conditions, including Duchenne muscular dystrophy (DMD) that is amenable to exon 51 skipping, if pre-authorization is approved, Exondys 51 (eteplirsen) will be authorized in doses up to 30 mg/kg every week. (52 infusions per year).

C. Authorization shall be reviewed at least every twelve months for documented benefit. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met. Specifically, documentation that the medication is providing clinical benefit, including disease stability or improvement, and lack of disease progression.

Position Statement

Summary

- Exondys 51 (eteplirsen) is an intravenous therapy indicated for the treatment of Duchenne muscular dystrophy (DMD) when there is a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. It was approved through the FDA Accelerated Approval Program based on an increase in dystrophin in skeletal muscles observed in some patients.
- A clinical benefit (e.g. prolongation of independent ambulation, improved quality of life, or prevention of disease progression and disability) of Exondys 51 (eteplirsen) has not been established. [1]

    * In two small studies in a total of 12 patients, Exondys 51 (eteplirsen) was shown to increase dystrophin levels. However, it has not been proven that an increase in dystrophin will translate to improved clinical outcomes, such as improved motor function.
    * The same studies failed to show that Exondys 51 (eteplirsen) helped improve performance on a 6-minute walk test, which is a clinically relevant measure of ambulatory ability.
- The U.S. Centers for Disease Control and Prevention (CDC) has developed general management guidelines for DMD. The CDC recommends corticosteroids and supportive care to slow disease progression. These guidelines were published prior to the approval to Exondys 51 (eteplirsen); thus, the use of Exondys 51 (eteplirsen) for DMD has not yet been addressed. [2,3]

Clinical Efficacy

- Evidence regarding the effect of Exondys 51 (eteplirsen) on dystrophin levels was inconclusive. Data is limited to a small, phase II trial (Study 201); an open-label, historically controlled, extension study (Study 202); and an ongoing, confirmatory phase III study (PROMOVI) with interim results. Although the preliminary evidence is promising, larger, well-controlled trials are needed to establish the safety and efficacy of Exondys 51 (eteplirsen) in Duchenne muscular dystrophy (DMD).
- In the pivotal trials (Study 201/202), 12 patients were initially randomized to receive either placebo or Exondys 51 (eteplirsen) 30 mg/kg/wk or 50 mg/kg/wk. There was a statistically significant percent increase (relative change) in dystrophin levels for the Exondys 51 (eteplirsen) treatment arms at 48 weeks. [4]
    * Dystrophin production is a surrogate biomarker of disease improvement with an unknown correlation to health outcomes. The use of dystrophin levels as a surrogate endpoint for DMD needs to be validated.
    * Only a relative change in dystrophin was reported, which could overestimate the difference observed. An analysis on the absolute change in dystrophin levels was not reported. An absolute increase in dystrophin levels has not been correlated to improved ambulation or muscle function and a minimal clinically important difference in dystrophin levels has not yet been established.
    * The muscle biopsies were processed and analyzed after unblinding occurred, which may have introduced bias into the results.
    * The study included patients from Europe. Since supportive care was not well-documented, the results may have been confounded by different standards of care.
    * The study became open-label after 12 weeks with subjects being compared to matched historical controls. Due to the observational nature of the trial, the cause and effect of Exondys 51 (eteplirsen) on dystrophin production cannot be established.
    * The FDA has acknowledged that findings from Study 201/202 are misleading and should be retracted. [5]

- After 180 weeks of treatment, the average dystrophin protein level in muscle tissue was found to be only 0.93% of the normal dystrophin level in found in healthy subjects. Experts have proposed that dystrophin levels greater than 10% of normal may be clinically meaningful; however, validation is needed. [1]
- In the ongoing confirmatory PROMOVI trial (open-label, observational), subjects treated with Exondys 51 (eteplirsen) for 48 weeks had an average dystrophin level of 0.44% of the normal dystrophin level in a healthy subject vs. 0.16% at baseline ($p < 0.05$). The median increase after 48 weeks was only 0.1%. [1]
- Exondys 51 (eteplirsen) has not been shown to improve distance walked on a 6-minute walk test (6MWT), which was the primary endpoint in Study 201/202. [4,6]
    * In Study 201, subjects in the Exondys 51 (eteplirsen) 30 mg/kg/wk arm actually performed worse on the 6MWT versus placebo at both 24 and 48 weeks. This was attributed to two subjects who had rapid disease progression after enrollment.
    * Study 202 showed no difference in performance on the 6MWT between the Exondys 51 (eteplirsen) arm compared to matched historical controls.
- Exondys 51 (eteplirsen) has not yet been shown to improve any clinical outcomes such as quality of life, prolongation of independent ambulation, or prevention of disease progression and disability.
- The change in forced vital capacity (FVC), an exploratory endpoint in the previously mentioned trials, was assessed after trials were completed, and compared to historical controls. There was a slight improvement in FVC decline, a surrogate endpoint. However, because the trial was not controlled, and efficacy analysis was based on a historical control, the data is considered insufficient to establish clinical utility
- The FDA Advisory Committee voted 7-6 against approval of Exondys 51 (eteplirsen) for DMD due to the lack of substantial evidence from adequate and well-controlled studies that Exondys 51 (eteplirsen) induces production of dystrophin to a level that is reasonably likely to predict clinical benefit. [5,7]

Safety

- Safety data for Exondys 51 (eteplirsen) is based on four years of clinical trial experience but in a very limited population (n = 12).
- The most common adverse reaction of Exondys 51 (eteplirsen) reported with an incidence of at least 35% were balance disorder and vomiting.
- Postmarketing safety studies on carcinogenicity are required in order to identify any unexpected serious risks associated with Exondys 51 (eteplirsen).

Table 1: Mutations Amenable to Exon 51 skipping			
17-50	28-50	36-50	45-50
19-50	29-50	37-50	47-50
21-50	30-50	38-50	48-50
23-50	31-50	39-50	49-50
24-50	32-50	40-50	50
25-50	33-50	41-50	52
26-50	34-50	42-50	52-58
27-50	35-50	43-50	52-61
52-63			

Cross References
BlueCross BlueShield Association Medical Policy, 5.01.27 - Treatment for Duchenne Muscular Dystrophy [June 2023]
BlueCross BlueShield Association Medical Policy, Gene Therapies for Duchenne Muscular Dystrophy [October 2023]
Vyondys 53, golodirsen, Medication Policy Manual, Policy No. dru606
Viltepso, viltolarsen, Medication Policy Manual, Policy No. dru640
Amondys 45, casimersen, Medication Policy Manual, Policy No. dru661
Elevidys, delandistrogene moxeparvovec, Medication Policy Manual, Policy No. dru754
Site of Care Review, Medication Policy Manual, Policy No. dru408

Codes	Number	Description
HCPCS	J1428	Injection, eteplirsen (Exondys 51), 10 mg
ICD-10	G71.0	Muscular dystrophy

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Revision History

Revision Date	Revision Summary
6/20/2024	Added Exondys to site of care (SOC) program (effective 10/1/2024).
12/7/2023	• Added quantity limit and reauthorization criteria (no change to intent) • Updated cross references.
12/9/2022	No criteria changes with this annual update.
1/20/2021	No criteria changes with this annual update.
1/22/2020	No criteria changes with this annual update.
12/13/2019	Added continuation of therapy (COT) criteria (no change to intent of coverage criteria).
1/31/2019	No criteria changes with this annual update. A table of mutations amenable to Exon 51 skipping was added to the appendix.
2/16/2018	No criteria changes with this annual update.
01/13/2017	New policy.

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Medication Policy Manual | **Policy No:** dru485

Topic: Spinraza, nusinersen | **Date of Origin:** February 17, 2017

Committee Approval Date: December 7, 2023 | **Next Review Date:** 2024

Effective Date: March 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Spinraza (nusinersen) is a medication used to treat certain types of spinal muscular atrophy (SMA), a rare genetic disorder that affects motor function. It is given by intrathecal (IT) injection directly into the spinal column.

Policy/Criteria

Most contracts require pre-authorization approval of Spinraza (nusinersen) prior to coverage.

I. Continuation of therapy (COT): Spinraza (nusinersen) may be considered medically necessary for COT when full policy criteria below are met, including quantity limit.

Please note: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.

II. New starts (treatment-naïve patients): Spinraza (nusinersen) may be considered medically necessary for treatment of spinal muscular atrophy (SMA) when there is clinical documentation (including, but not limited to chart notes) that criteria A through E below are met.

A. A diagnosis of **classic SMA** (5q SMA) is established by, or in consultation with a pediatric neuromuscular specialist (pediatric neurologist or rehabilitation doctor)

AND

B. One of the following:

1. Documentation showing SMA-associated symptoms before 12 years of age (also known as SMA type 1, type 2, or type 3)

OR

2. Presymptomatic SMA with confirmation of 2 or 3 copies of SMN2

AND

C. Genetic confirmation of a diagnosis of classic SMA, with a loss of, or defect in, the survival motor neuron (SMN) 1 gene.

AND

D. Prior to starting Spinraza (nusinersen) therapy, documentation showing baseline motor function, with objective function-based testing (such as with a HINE or CHOP-Intend score).

AND

E. Documentation of comprehensive SMA care, including physical therapy, respiratory care, and nutrition support as part of the patient's care plan.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Spinraza (nusinersen) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Spinraza (nusinersen) may be authorized for up to twelve months, for a maximum of 4 doses (12 mg per dose) in a 64-day period, based on loading doses on Days 1, 15, 29, 59, then a maximum of 1 dose (12 mg per dose) in a 4-month period (based on dosing on days 179 and 299), for a total of 6 doses in a 299-day period. NOTE: *If the loading dose regimen (standard timing) is interrupted, doses will be approved on a case-by-case basis per the FDA label, if there is detailed documentation as to prior doses and dates of administration.*

C. After initial authorization, Spinraza (nusinersen) may be reauthorized for a maximum of three doses (12 mg per dose) every 12 months [based on dosing of 12 mg every 4 months]. Authorization shall be reviewed at least every 12 months when criteria a and b are met:

a. Documentation (including, but not limited to chart notes) is provided showing current medical necessity criteria are met, including comprehensive care by, or in consultation with, a neuromuscular specialist.

AND

b. Documentation (including, but not limited to chart notes) is provided showing that the medication is effective, including documentation of clinically significant improvement of motor function or stabilization of motor function loss, which **must** include clinical documentation of a physical assessment, motor function function-based testing, and need for medical intervention related to SMA symptoms, relative to baseline (and/or previous authorization period). Overall motor function must be improved/superior relative to that projected for the natural course of SMA.

IV. Spinraza (nusinersen) is considered investigational when used for all other conditions or settings, including but not limited to:

A. Other types of classic SMA not specified above

B. Non-5q SMA (SMA due to genetic abnormalities other than on chromosome 5q)

C. Combination use with Evrysdi (risdiplam).

V. Spinraza (nusinersen) is considered not medically necessary when used after a Zolgensma (onasemnogene abeparvovec-xioi) infusion.

Position Statement

Summary

- Spinraza (nusinersen) is an antisense oligonucleotide (ASO), FDA approved for treatment of spinal muscle atrophy (SMA) due to a mutation of the SMN1 protein on the 5q chromosome ("classic SMA").
- SMA is a rare condition, with a genetic defect which leads to low the survival motor neuron (SMN) protein, progressive loss of motor neuron function, hypotonia, weakness, and chronic respiratory insufficiency.
  * Children with the most severe form (SMA type 1) have symptoms before the age of 6 months and do not reach motor milestones (like sitting unassisted). SMA type 1 is also called "infantile SMA" or Werdnig-Hoffman disease.
  * Later onset SMA (such as SMA type 2 or 3) is diagnosed later (symptom onset after 6 months of age), when a child fails to meet a motor milestone. SMA type 2 is also called Dubowitz disease. SMA type 3 is also called Kugelberg-Welander disease.

- Genetic testing is required to confirm of a diagnosis of classic SMA (5q SMA) and to rule out other causes of spinal muscular atrophy. Onset of SMA symptoms (such as failure to meet motor milestones) differentiates SMA types 1, 2, and 3. SMA type 1 has onset of symptoms prior to 6 months of age and is the most severe, progressive form of SMA.
- In clinical trials of young children (< 7 months of age) with SMA type 1 and presymptomatic SMA with 2 or 3 copies of SMN2, Spinraza (nusinersen) improved the ability to achieve motor milestones (such as head control, sitting, ability to kick in supine position, rolling, crawling, standing and walking), versus what is seen with the natural progression of SMA.
- In clinical trials of later-onset SMA (type 2 and type 3), Spinraza (nusinersen) improved motor function scores and slowed loss of motor function, versus what is seen with the natural progression of SMA.
- The safety and effectiveness of Spinraza (nusinersen) in conditions other than SMA types 1, 2, or 3 have not been established. Trials of nusinersen included patients up to 12 years of age, but not older. Therefore, the use of nusinersen for SMA type 4 is investigational.
- The use of Spinraza (nusinersen) after Zolgensma (onasemnogene abeparvovec-xioi) for patients with an incomplete response, defined as persistent SMA symptoms, may be effective. However, the use of Spinraza (nusinersen) for residual SMA symptoms after Zolgensma (onasemnogene abeparvovec-xioi) is considered not medically necessary. Given the very high cost of the Zolgensma (onasemnogene abeparvovec-xioi) and Spinraza (nusinersen) therapies, we are unable to cover both treatment options.
- Guidelines recommend aggressive, comprehensive supportive care.
- The recommended dose of Spinraza (nusinersen) is 12 mg injected intrathecally (IT), with four loading doses in 58 days (every 14 days for three doses, then in 30 days), then 12 mg IT every four months maintenance. The safety and effectiveness of higher doses have not been established. [1]

Disease Background [2-4]

- Spinal muscular atrophy (SMA) is a SMA is a rare, hereditary disease characterized by loss of motor neurons in the spinal cord and lower brain stem, and results in severe and progressive muscular atrophy, hypotonia, diffuse symmetric weakness, and restrictive lung disease. Patients with the most severe type of SMA can become paralyzed, never sit or walk, and have difficulty breathing and swallowing due to bulbar muscle weakness (requiring mechanical ventilation, gastrostomy tube enteral feeding, and nursing care).
- Classic SMA is caused by a loss of, or defect in, the survival motor neuron (SMN) 1 gene, with homozygous SMN1 exon 7 deletion and/or deletion and mutation on other alleles, resulting in inadequate production of SMN protein.
    * This protein is needed for the proper maintenance of motor neurons. SMN2 may be present, but mostly produces SMN protein lacking in exon 7, a less stable protein, and unable to compensate for the lack of SMN1.
    * SMN2 copies may be increased and produce SMN protein for milder forms of SMA (such as type 2 or 3).
- The incidence of SMA is approximately 4 to 10 per 100,000 live births (about 400 births in the U.S. per year).

- There is wide variability in age of onset, symptoms and rate of progression. Earlier onset is generally associated with more severe disease. The severity of SMA correlates with the amount of SMN protein.
- SMA Type 1 (infantile SMA, Werdnig-Hoffman disease; "non-sitters") is the most common and most severe form of SMA, with early symptom onset (< 6 months of age) and rapid progression to flaccid paralysis and restrictive progressive respiratory insufficiency. Most infants die without respiratory support within 1 year. Historic average time to death or full-time noninvasive ventilation (> 16 hours/day) is 13.5 months.
- Later onset SMA (type 2 and 3) patients produce greater amounts of SMN protein, have a later onset, and less severe. Outcome depends on severity of weakness at presentation; early onset correlates with greater weakness.
    * SMA Type 2 (intermediate form, Dubowitz disease; "sitters") present between 6 to 18 months, may reach motor milestone more slowly, can sit unassisted but lose this ability with time, and never walk.
    * SMA Type 3 (mild form, Kugelberg-Welander disease; "standers") presents after one year of age. Legs are affected more than arms. All walk but many lose ability to walk with time (highly variable).

Clinical Efficacy

- One phase 3 randomized, double-blinded, sham-controlled trial (ENDEAR) evaluated Spinraza (nusinersen) vs. sham injection in SMA1 in children started at less than 7 months of age. [4,5]
    * All subjects had onset of SMA symptoms prior to the age of 6 months and a diagnosis genetically confirmed.
    * Motor milestones were evaluated based on the Hammersmith Infant Neurological Exam (HINE) categories (in the modified section 2).
    * "Motor milestone responder" was defined as more categories of improvement than worsening, based on the modified section 2 of the HINE.
    * The proportion of subjects who were motor milestone responders was significantly higher with Spinraza (nusinersen) than placebo, based on a preplanned interim analysis. (n=82).
- One phase 3 randomized, double-blinded, sham-controlled trial (CHERISH) evaluated Spinraza (nusinersen) vs. sham injection (n=126) in later-onset SMA (types 2 and 3) in children started at 2 to 12 years of age. [4,7]
    * All subjects had onset of SMA symptoms at > 6 months of age, were between the age of 2 and 12 years of age at the time of screening for the trial, and the diagnosis of SMA was genetically confirmed. All subjects could sit independently, but never had the ability to walk independently.
    * Motor function was evaluated based on the Hammersmith functional motor scale expanded (HFMSE) score. A change from baseline of > 3 points was considered a responder.
    * Subjects in the Spinraza (nusinersen) arm had a significantly higher change in HFMSE versus those in the placebo arm. (+5.9 points, placebo-subtracted). Key secondary endpoints that were statistically higher with nusinersen vs. placebo

included percent of HFMSE responders (56.8% vs. 26.3%; p=0.006) and number of new motor milestones (+0.2 vs. -0.2; p<0.0001). However, more meaningful health outcomes of standing along and walking without assistance were not different between treatment arms, though secondary outcomes and not powered for statistical significance.

- Interim efficacy and safety data from an ongoing phase 2 open-label trial evaluated Spinraza (nusinersen) in presymptomatic SMA in children with 2 or 3 copies on SMN2 and started at less than 6 weeks of age
    * At the time of the data cut, patients ranged from 25.7 to 45.4 months of age, with a median 2.9 years since the first administration.
        - All enrolled patients were alive, and none required permanent ventilation.
        - Mean CHOP INTEND scores were 62.1 and 63.4 for those with two copies and 3 copies of SMN2, respectively. A max score of 64 was achieved by 10/15 (66%) and 10/10 (100%) with two and three copies of SMN2, respectively
        - All enrolled patients (25/25) achieved the ability to sit without support, 92% (23/25) achieved the ability to walk with assistance, and 88% (22/25) achieved the ability to walk independently.
- Long-term extension trials are ongoing to establish the long-term safety and efficacy of Spinraza (nusinersen) for health outcomes such as ability to stand, walk, and need for invasive or non-invasive ventilation. [4]
- Guidelines recommend maximizing aggressive multidisciplinary care, including orthopedic/rehabilitation, pulmonary, and gastrointestinal/nutrition care, along with psychological and social support. Therapy should be tailored to the patient functional level: nonsitter, sitter, or walker. [6]

Investigational Uses

- There is insufficient evidence to establish the efficacy of Spinraza (nusinersen) for the treatment of very late onset SMA (SMA type 4 or adult onset). Trials excluded patients over the age of 12.

Cross References
BlueCross BlueShield Association Medical Policy, 5.01.28 - Treatment for Spinal Muscular Atrophy. [April 2023]
Zolgensma, onasemnogene abeparvovec-xioi, Medication Policy Manual, Policy No. dru591
Evrysdi, risdiplam, Medication Policy Manual, Policy No. dru647

Codes	Number	Description
HCPCS	J2326	Injection, nusinersen (Spinraza), 0.1 mg
ICD-10	G12.0	Infantile spinal muscular atrophy, type I [Werdnig-Hoffmann]
ICD-10	G12.1	Other inherited spinal muscular atrophy Includes: - Adult form spinal muscular atrophy - Childhood form, type II spinal muscular atrophy - Juvenile form, type III spinal muscular atrophy [Kugelberg-Welander]

Appendix 1 – SMA Subtypes

Clinical Subtype	% of cases	Usual # SMN2 copies	Symptom onset	Life expectancy	Motor development [a]
Type 0	Very rare	1	In utero	Die shortly after birth	None
Type 1	58	2	≤ 6 months	≤ 24 months	Never able to sit unassisted.
Type 2	29	80% have 3 copies	≤ 18 months	70% alive at 25 years	Unable to walk without assistance.
Type 3	13	80% have 4 copies	18-36 months (3-10 years)	May be normal	Able to stand and to walk without assistance, but lose ability as the disease progresses
Type 4	<5	≥4	20-30 years	Normal	Ambulatory. May experience mild muscle weakness

[a] Motor milestones: ability to kick, head control, rolling, sitting, crawling, and standing

Adapted from the Spinraza FDA Medical Review [5]

References

1. Spinraza (nusinersen) injection for intrathecal use [package insert]. Cambridge, MA: Biogen, Inc; February 2023.
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5. FDA Center for Drug Evaluation and Research (CDER). Medical Review. NDA 209531; Spinraza (nusinersen). 12/23/2016. [cited 1/25/2017]; Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/209531Orig1s000TOC.cfm

   Wang, CH, Finkel, RS, Bertini, ES, et al. Consensus statement for standard of care in spinal muscular atrophy. Journal of child neurology. 2007 Aug;22(8):1027-49. PMID: 17761659
6. Medical information [data on file]. May 5, 2017. Cambridge, MA: Biogen; Data reviewed May 2017

Revision History

Revision Date	Revision Summary
12/7/2023	No criteria changes with this annual review.
12/9/2022	No criteria changes with this annual review.
1/20/2021	• Broadened prescriber requirement to include non-pediatric neuromuscular specialists. • Added combination use with Evrysdi (risdiplam) to investigational uses.
4/22/2020	Add coverage criteria for presymptomatic SMA in patients with 2 or 3 copies of SMN2. Added COT language.
4/25/2019	Added the use of Spinraza (nusinersen) after Zolgensma (onasemnogene abeparvovec-xioi) infusion to be considered not medically necessary.
1/31/2019	Investigational uses (presymptomatic SMA) updated with this annual update. Clarified documentation requirements (no change to intent).
2/16/2018	No criteria changes with this annual update.
7/14/2017	Add coverage criteria for later-onset SMA (types 2 and 3).
2/17/2017	New policy.

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Medication Policy Manual **Policy No:** dru488

Topic: Pituitary Disorder Therapies **Date of Origin:** February 17, 2017

- Isturisa, osilodrostat
- Lanreotide acetate (generic, Somatuline Depot)
- Mycapssa, octreotide
- Recorlev, levoketoconazole
- Sandostatin LAR Depot, octreotide LAR
- Signifor, pasireotide
- Signifor LAR, pasireotide LAR
- Somavert, pegvisomant

Committee Approval Date: September 19, 2024 **Next Review Date:** 2025

Effective Date: December 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

The medications included in this policy are used to treat pituitary disorders, such as acromegaly, Cushing syndrome, and Cushing's disease. These pituitary disorders are typically the result of excessive growth hormone or cortisol production.

Policy/Criteria

Most contracts require pre-authorization approval of pituitary disorder therapies prior to coverage.

I. Continuation of therapy (COT): Pituitary Disorder therapies may be considered medically necessary for COT when criterion A or B below is met.

A. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

OR

B. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note: *Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve) patients: Pituitary Disorder therapies may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) of use for one of the following indications listed in the criteria below and coverage criteria are met.

Diagnosis	Coverage Criteria	Coverable Products(s)
Acromegaly	When criteria 1 and 2 are met: **1.** Documented inadequate response to surgery and/or radiation **OR** surgery/radiation is documented as not an option. **AND** **2.** ***[For lanreotide (generic, Somatuline Depot), Signifor LAR (pasireotide LAR), Mycapssa (octreotide), and Somavert (pegvisomant)]:*** For adults only: Treatment with Sandostatin LAR Depot (octreotide LAR) has been ineffective, not tolerated, or is contraindicated.	• Lanreotide (generic, Somatuline Depot) • Mycapssa (octreotide) • Sandostatin LAR Depot (octreotide LAR) • Signifor LAR (pasireotide LAR) • Somavert (pegvisomant)
Carcinoid syndrome	When criteria 1 and 2 are met: **1.** Flushing and/or diarrhea due to a neuroendocrine tumor (NET), including carcinoid tumors (such as GI tract, lung, and thymus) and VIPoma. **AND** **2.** ***[For lanreotide (generic, Somatuline Depot)]***: Treatment with Sandostatin LAR Depot (octreotide LAR) has been ineffective, not tolerated, or is contraindicated	• Lanreotide (generic, Somatuline Depot) • Sandostatin LAR Depot (octreotide LAR)

Diagnosis	Coverage Criteria	Coverable Products(s)
Cushing's disease (CD)	When criteria 1 and 2 are met: **1.** Pituitary surgery is not an option or has not been curative. **AND** **2.** At least one prior lower-cost CD medication treatment option was not effective unless all are contraindicated (see *Appendix 1*).	• Isturisa (osilodrostat) • Signifor (pasireotide) • Signifor LAR (pasireotide LAR)
Endogenous Cushing's syndrome	When criteria 1, 2, and 3 are met: **1.** Patient has a documented cause for endogenous Cushing's syndrome (see *Appendix 2*). **AND** **2.** Surgical resection of primary tumor is not an option or has not been curative. **AND** **3.** Prior generic ketoconazole therapy was ineffective, defined as persistent urinary free cortisol greater than 50 µg/day despite at a maximized dose of ketoconazole 1200 mg/day. **PLEASE NOTE:** the intent of this criterion is NOT met with intolerance of ketoconazole or use of lower doses.	• Recorlev (levoketoconazole)
GEP-NET [a]	When criteria 1 and 2 are met: **1.** When unresectable, locally advanced or metastatic. **AND** **2.** ***[For lanreotide (generic, Somatuline Depot)]:*** Treatment with Sandostatin LAR Depot (octreotide LAR) has been ineffective, not tolerated, or is contraindicated.	• Lanreotide (generic, Somatuline Depot) • Sandostatin LAR Depot (octreotide LAR)

[a] Gastroentero-pancreatic neuroendocrine tumors (GEP-NET), such as gastrointestinal tract, lung, thymus, or pancreatic neuroendocrine tumors

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Pituitary Disorder Therapies coverable only under the medical benefit (for provider-administration) and the pharmacy benefit (for self-administration), as outlined in *Table 1*.

B. When pre-authorization is approved, pituitary disorder therapies will be covered in the quantities outlined in *Table 1*.

C. **Recorlev (levoketoconazole) only, initial** authorization **shall** be reviewed at 6 months. Clinical documentation (including but not limited to chart notes) must be provided indicating that urinary free cortisol levels have normalized below the upper limit of normal (≤50 µg/day).

D. **A**uthorization for all other pituitary disorder therapies listed below in *Table 1* and **continued** authorization of Recorlev (levoketoconazole) **may** be reviewed annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement. For **Signifor (pasireotide) and Recorlev (levoketoconazole)**, clinical documentation indicating that urinary free cortisol levels are within normal limits must be provided.

Table 1:

Pituitary Disorder Therapies: Coverable Indications, Quantity Limits, and Coverage/Administration Product	**Coverable Indications and Quantity Limits**	**Coverage/Administration**
Lanreotide (generic, Somatuline Depot)	**1. Acromegaly:** **a. Initial authorization:** Up to one 90-mg kit every 4 weeks. **b. Dose escalations:** Up to one 120-mg kit every 4 weeks may be authorized for members who show inadequate response after 3 months on 90 mg every 4 weeks. **2. GEP-NET:** Up to one 120-mg kit every 4 weeks. **3. Carcinoid syndrome:** Up to one 120-mg kit every 4 weeks.	Medical benefit (Provider-administered)
Recorlev (levoketoconazole)	**Endogenous Cushing's syndrome:** Up to 1200 mg daily based on a maximum dose of 600 mg twice daily.	Pharmacy benefit (Self-Administered)
Mycapssa (octreotide)	**Acromegaly:** Up to 120 capsules per 30 days.	Pharmacy benefit (Self-Administered)
Sandostatin LAR Depot (octreotide LAR)	**1. Carcinoid syndrome** (including carcinoid tumors, VIPomas, or GEP-NET): **a. Initial authorization:** Up to 40 mg every 4 weeks. **b. Dose escalation:** Doses greater than 40 mg every 4 weeks may be authorized in patients who continue to have symptoms despite receiving 40 mg every 4 weeks. **2. Acromegaly:** Up to 40 mg every 4 weeks.	Medical benefit (Provider-administered)
Isturisa (osilodrostat)	**Cushing's Disease:** Up to 60 mg daily based on a maximum dose of 30 mg twice daily.	Pharmacy benefit (Self-administered)

Pituitary Disorder Therapies: Coverable Indications, Quantity Limits, and Coverage/Administration Product	Coverable Indications and Quantity Limits	Coverage/Administration
Signifor (pasireotide)	**1. Cushing's Disease** **a. Initial authorization:** Up to 60 of the 0.6-mg ampules every month. **b. Dose escalation:** Up to 60 of the 0.9-mg ampules every month may be authorized for members who show inadequate response to 0.6-mg twice daily.	Pharmacy benefit (Self-administered)
Signifor LAR (pasireotide LAR)	**1. Acromegaly** **a. Initial authorization:** Up to one 40-mg kit every 4 weeks. **b. Dose escalation:** Up to one 60-mg kit every 4 weeks may be approved for members who show inadequate improvement on 40 mg every 4 weeks. **2. Cushing's Disease** **a. Initial authorization:** Up to one 10-mg kit every 4 weeks. **b. Dose escalation:** Up to one 40-mg kit every 4 weeks may be approved for members who show inadequate response to 10 mg every 4 weeks.	Medical benefit (Provider-administered)
Somavert (pegvisomant)	**Acromegaly:** A one-time loading dose of 40 mg, followed by up to 30 of the 30-mg vials per month.	First dose ONLY: Medical benefit (Provider administered) *(first dose under provider supervision)* Subsequent doses: Pharmacy benefit (Self-administered)

IV. Not Medically Necessary Uses

A. Pituitary disorder therapies [as listed in Table 1, including, but not limited to, Sandostatin LAR (octreotide LAR)] are considered not medically necessary when used for chemotherapy-induced diarrhea.

V. The pituitary disorder therapies included in this policy are considered investigational when used for all other conditions not listed above in the coverage criteria.

Position Statement

Summary

- The intent of this policy is to allow for coverage of pituitary disorder therapies (as listed on page 1) for the FDA indications after use of step therapies (where appropriate, as detailed in the coverage criteria), for up to the doses supported in clinical trials.
- The medications included in this policy are either somatostatin analogs, growth hormone (GH) receptor antagonists, or cortisol-blocking therapies.
    * Somatostatin is a natural hormone that lowers excessive GH levels. Somatostatin analogs [e.g., lanreotide, octreotide, and pasireotide] work by binding to somatostatin receptors, thereby suppressing GH secretion. They also inhibit adrenocorticotropic hormone (ACTH) secretion, which leads to decreased cortisol secretion.
    * GH receptor antagonists [(Somavert (pegvisomant)] work by blocking endogenous GH from binding to GH receptors, which can lead to decreased serum insulin-like growth factor-I (IGF-I) concentrations.
    * Cortisol-blocking therapies, such as ketoconazole (generic), Recorlev (levoketoconazole), and Isturisa (osilodrostat), work by inhibition of cortisol synthesis via various pathways.
- Pituitary disorder therapies have data from randomized, controlled trials to support their use in FDA-approved indications, endorsement from guidelines as standard of care therapy, and years of clinical experience. Uses include:
    * Acromegaly
    * Cushing's syndrome (CS), including Cushing's disease
    * Advanced gastrointestinal tract, lung, thymus, or pancreatic neuroendocrine tumors (GEP-NET),
    * Carcinoid syndrome (flushing and/or diarrhea) from neuroendocrine tumors (NET), including but not limited to pancreatic neuroendocrine tumors which secretes vasoactive intestinal peptide (VIP), also known as VIPoma.
- *For acromegaly*:
    * Somatostatin analogs, such as octreotide (generic, Sandostatin LAR Depot), provide the best value for treatment of acromegaly.
    * Guidelines recommend transsphenoidal surgery as first-line treatment for most patients with acromegaly.
    * Somatostatin analogs are recommended as second-line options.
    * Mycapssa (octreotide) delayed release is an oral formulation of octreotide that is FDA approved for the treatment of acromegaly. Unlike other forms of octreotide, it is only FDA approved for acromegaly.
- *For Cushing's syndrome (CS), including Cushing's disease*:
    * Guidelines recommend surgical resection as first-line treatment for Cushing's.
    * Cortisol-blocking therapies and pituitary-directed medications are recommended as second-line options.

- Generic ketoconazole provides the best value for CS if surgical intervention is not an option or has failed. Higher-cost options are coverable only when lower-cost options are ineffective.
- *For advanced GEP-NET:*
    * Lanreotide (generic, Somatuline Depot) is approved and used for GEP-NET
    * Sandostatin LAR Depot (octreotide LAR) is not FDA-approved for GEP-NET; however, its use is supported by clinical trials and all three somatostatin analogs, including lower-cost Sandostatin (octreotide) and Sandostatin LAR Depot (octreotide LAR), are guideline recommended treatment options for GEP-NET [National Comprehensive Cancer Network (NCCN)].
- *For carcinoid syndrome (flushing and/or diarrhea) from carcinoid tumors and NET, including VIPoma:*
    * Sandostatin LAR Depot (octreotide LAR) and lanreotide (Somatuline Depot, brand only) are approved and used for carcinoid syndrome.
    * However, all three somatostatin analogs, including lower-cost Sandostatin (octreotide) and Sandostatin LAR Depot (octreotide LAR), are guideline recommended treatment options for carcinoid syndrome (flushing and diarrhea associated with carcinoid tumors).
- NCCN guidelines for neuroendocrine and adrenal tumors recommend either Sandostatin LAR Depot (octreotide LAR) or lanreotide (generic, Somatuline Depot) for the treatment of GEP-NETs and Carcinoid syndrome. [7] The guidelines do not give preference to either agent. Between the two long-acting options, Sandostatin LAR Depot (octreotide LAR) provides the best value.
- The recommended initial dosing for Sandostatin LAR Depot (octreotide LAR) for acromegaly or for symptomatic control in carcinoid tumors or VIPomas is 20 mg intramuscular injection given by a health care provider once every 4 weeks. Dosing adjustments should be made after two or three months, based on response and tolerability, up to a maximum dose of 40 mg every 4 weeks for acromegaly and 30 mg every 4 weeks for carcinoid tumors or VIPomas. Although the use of Sandostatin LAR Depot (octreotide LAR) for GEP-NET is not an FDA-approved use, the dose of 20 mg per month is a suggested starting dose per guidelines and expert input, to prevent excessive dosing and associated adverse events.
    * The safety and efficacy of doses exceeding the maximum dosage in the FDA-approved labeling have not been established in clinical trials; however, the NCCN guidelines suggest higher doses may be of value in GEP-NET or VIPoma and carcinoid syndrome when starting doses are insufficient for disease control, as detailed in the coverage criteria.
- For other products, including lanreotide (generic, Somatuline Depot), the safety and efficacy of doses exceeding the maximum dosage in the FDA-approved labeling have not been well established in clinical trials.
- The safety and efficacy of conditions not included in the FDA-approved labeling have not been established in clinical trials.

Clinical Efficacy

ACROMEGALY

Octreotide [1-3]

- A single, high-quality meta-analysis found that in patients taking Sandostatin LAR Depot (octreotide LAR) who were not preselected for somatostatin analog responsiveness, 54% met GH efficacy criteria and 63% had IGF-I normalization.
- Mycapssa (octreotide) was evaluated in one placebo-controlled trial in patients with acromegaly. The study demonstrated that Mycapssa (octreotide) produced higher rates of IGF-1 normalization compared to placebo.

Lanreotide (generic, Somatuline Depot) [4-6]

- One double-blind, controlled study evaluated the efficacy of lanreotide (generic, Somatuline Depot) 60 mg, 90 mg, and 120 mg compared to placebo in patients with acromegaly.
    * After 4 weeks, 63% of patients in the pooled lanreotide (generic, Somatuline Depot) arms had a > 50% decrease in mean GH compared to 0% in the placebo arm.
- One open-label uncontrolled trial evaluated the efficacy of lanreotide (generic, Somatuline Depot) 90 mg on IGF-1 levels in patients with acromegaly.
    * After 48 weeks, 43% of patients achieved normal age-adjusted IGF-1 concentrations. The mean IGF-1 concentration after treatment was 1.3 times the upper limit of normal (ULN) compared to 2.5 times ULN at baseline.
    * The reduction in IGF-1 concentrations correlated with a corresponding decrease in mean GH concentrations. After 48 weeks, 38% of patients had both normal IGF-1 concentrations and a GH concentration of ≤ 2.5 ng/mL, and 27% of patients had both normal IGF-1 concentrations and a GH concentration of <1 ng/mL.
- A single, low-quality meta-analysis evaluated head-to-head studies between Sandostatin LAR Depot (octreotide LAR) and lanreotide (generic, Somatuline Depot).
    * A GH level < 2.5 µg/L was achieved in 65.3% of patients on Sandostatin LAR Depot (octreotide LAR) versus 59.5% of patients on lanreotide (generic, Somatuline Depot).
    * Normalization of IGF-I was achieved in 46.7% of patients on Sandostatin LAR Depot (octreotide LAR) versus 52.7% of patients on lanreotide (generic, Somatuline Depot).
    * Biochemical control was achieved in 46% of patients on Sandostatin LAR Depot (octreotide LAR) versus 41.9% of patients on lanreotide (generic, Somatuline Depot).

Signifor LAR (pasireotide LAR) [7 8]

- A head-to-head, superiority trial evaluated the efficacy of Signifor LAR (pasireotide LAR) 40mg compared to Sandostatin LAR Depot (octreotide LAR) over a 12-month period in treatment-naïve patients with acromegaly.

    * The primary endpoint was a biochemical response (GH < 2.5 µg/L and normalized IGF-I adjusted for age and gender). However, current guidelines target a GH level < 1 µg/L.
    * Biochemical response was achieved in 31.3% of patients in the Signifor LAR (pasireotide LAR) arm and 19.2% of patients in the Sandostatin LAR Depot (octreotide LAR) arm. However, the maximum dose of Sandostatin LAR Depot (octreotide LAR) used in the trial was only 30 mg compared to the FDA-approved maximum of 40 mg.
- A randomized, controlled trial evaluated the efficacy of two strengths of Signifor LAR (pasireotide LAR) compared to continued treatment with Sandostatin LAR Depot (octreotide LAR) and Somatuline LAR (lanreotide) over a 6-month period in patients who were unable to achieve biochemical control with either Sandostatin LAR Depot (octreotide LAR) or Somatuline LAR (lanreotide).
    * The primary endpoint was a biochemical response (GH < 2.5 µg/L and normalized IGF-I adjusted for age and gender). Current guidelines target a GH level < 1 µg/L.
    * Biochemical response was achieved in 15% of patients in the Signifor LAR (pasireotide LAR) 40mg arm, 20% of patients in the Signifor LAR (pasireotide LAR) 60mg arm, and 0% of patients in the active control arm.
    * The maximum dose of Sandostatin LAR Depot (octreotide LAR) used in the trial was only 30 mg compared to the FDA-approved maximum of 40 mg.

Somavert (pegvisomant) [9 10]

- A randomized, double-blinded, placebo-controlled, 12-week study evaluated the safety and efficacy of Somavert (pegvisomant) 10 mg, 15 mg, or 20 mg in patients with acromegaly.
    * The mean serum IGF-I concentration decreased from baseline by 4.0%, 26.7%, 50.1%, and 62.5% in the placebo, 10 mg, 15 mg, and 20 mg arms, respectively. This difference was significant in all treatment arms compared to placebo.
    * Normalization of serum IGF-I concentrations were achieved in 10%, 54%, 81%, and 89% of subjects in the placebo, 10 mg, 15 mg, and 20 mg arms, respectively.
    * In patients treated with Somavert (pegvisomant) 15 mg or 20 mg daily, there were significant decreases in ring size, soft-tissue swelling, the degree of excessive perspiration, and fatigue.
    * The total score for signs and symptoms of acromegaly decreased significantly in all groups receiving Somavert (pegvisomant).

Guidelines [11]

- The Endocrine Society clinical guidelines for acromegaly recommend transsphenoidal surgery as first-line treatment for most patients.
    * Pharmacological treatment with a somatostatin analog or Somavert (pegvisomant) is recommended as the initial adjuvant medical therapy.
    * In patients with mild disease, a trial of a dopamine agonist, such as cabergoline, is recommended as the initial adjuvant medical therapy.

* Patients with an inadequate response to a somatostatin analog should try adding cabergoline or Somavert (pegvisomant).

GASTROENTEROPANCREATIC NEUROENDOCRINE TUMORS (GEP-NET) [4 5 12-15]

- The CLARINET trial (multicenter, randomized, double-blind, controlled) evaluated the efficacy of lanreotide (generic, Somatuline Depot) 120 mg in patients with GEP-NETs compared to placebo.
  * Patients were required to have non-functioning tumors without hormone-related symptoms. The majority (69%) of the study population had grade 1 tumors.
  * The primary endpoint was progression-free survival (PFS).
  * Patients in the lanreotide (generic, Somatuline Depot) arm had a statistically significant improvement in PFS compared placebo (median not reached vs. median of 18.0 months).
- The PROMID trial showed an improvement in time to tumor progression in neuroendocrine tumors of the midgut with Sandostatin LAR Depot (octreotide LAR) compared to placebo (14.3 months vs. 6 months).
- The National Comprehensive Cancer Network (NCCN) Neuroendocrine and Adrenal Tumors guideline list Sandostatin LAR Depot (octreotide LAR) and lanreotide (generic, Somatuline Depot) as category 2A recommendation for gastrointestinal tract, lung, thymus, or pancreatic neuroendocrine tumors (GEP-NET).
- The CLARINET FORTE phase 2 open-label single arm trial showed dosing of lanreotide (generic, Somatuline Depot) at every 14-day intervals in patients with previous disease progression on every 28-day dosing of lanreotide. The primary endpoint of progression free survival (PFS) was 8.3 months in the midgut and 5.6 in the pNEt cohorts. PFS is a surrogate endpoint and is not directly related to true clinical benefit such as overall survival and quality of life. There was a lack of comparator in the trial as well as a small sample size. The evidence of true clinical benefit due to dose interval increase rather than moving on to another treatment option in patients with pancreatic or midgut neuroendocrine tumors is insufficient at this time.
- NCCN guidelines state that octreotide (usually 150mcg-250mcg three times daily) can be added to Sandostatin LAR Depot (octreotide LAR) or lanreotide (generic, Somatuline Depot) for rapid relief of symptoms or breakthrough symptoms.
- Additional prospective randomized controlled studies are needed to establish the safety and efficacy of above label dosing for Sandostatin LAR Depot (octreotide LAR) and lanreotide (generic, Somatuline Depot).

CUSHING'S DISEASE (CD)

- Surgery is the mainstay, first-line treatment option for many patients with Cushing's disease. Cortisol-blocking therapies and pituitary-directed medications are recommended as second-line options.

- There are various medication treatment options, which differ based on mechanism of action, as well as cost.
    * Generic ketoconazole provides the best value for CD if surgical intervention is not an option or has failed. High-cost options are coverable only when lower-cost options (as listed in Appendix 1) are ineffective, as detailed in the coverage criteria.
    * High-cost options include, but are not limited to, Recorlev (levoketoconazole), Isturisa (osilodrostat), Signifor (pasireotide), Signifor LAR (pasireotide LAR). The evidence for the use of these high-cost options is detailed below.

Signifor (pasireotide) [7 16 17]

- There is low-quality evidence that Signifor (pasireotide) has any clinically relevant effect on improving symptoms in patients with CD. The effects of Signifor (pasireotide) on long-term consequences of CD, including cardiovascular outcomes, bone loss, or death, have not been studied.
- The evidence of efficacy for Signifor (pasireotide) in CD is of poor quality because it is based on a single, unblinded, uncontrolled (no comparator) trial.
    * The trial enrolled adult patients with confirmed CD (pituitary tumor) who had recurrent or persistent disease despite tumor resection or who were not candidates for surgery. Subjects enrolled in the trial had a mean urinary free cortisol (UFC) level of at least 1.5 times the upper limit of normal.
    * The trial evaluated three different doses of Signifor (pasireotide): 0.3 mg, 0.6 mg, or 0.9 mg subcutaneously twice daily.
    * The primary endpoint of the study was the proportion of subjects with normalized UFC levels at month 6. Additional endpoints included proportion of subjects with normalized UFC levels at month 3 and 12.
    * At month 3, 16% and 28% of subjects had normalization of UFC levels in the 0.6 mg and 0.9 mg treatment arms, respectively. At month 6, 16% and 29% had normalized UFC levels, respectively; and at month 12, UFC levels had normalized in 13% and 25% of subjects, respectively.
    * Subjects with lower baseline UFC levels were more likely to achieve normalization of UFC.

Signifor LAR (pasireotide LAR) [18 19]

- A phase 3 trial evaluated the efficacy of Signifor LAR (pasireotide LAR) 10mg compared to Signifor LAR (pasireotide LAR) 30mg every 4 weeks for 12 months in persistent, recurrent, or non-surgical patients with Cushing's disease.
    * The primary endpoint was the proportion of patients in each group with a mean urinary free cortisol (mUFC) concentration of less than or equal to the ULN at month 7.
    * The primary efficacy endpoint was met by 31 (41.9%) of patients in the 10 mg group and 31 (40.8%) of patients in the 30 mg group.

* The maximum dose of Signifor LAR (pasireotide LAR) used in the trial was 30 mg and 40mg in the 10 mg and 30 mg treatment arms, respectively.

Isturisa (osilodrostat)[20]

- Isturisa (osilodrostat) was evaluated in one phase 3 randomized, withdrawal study known as LINC-3. The study included patients with CD who previously had pituitary surgery or irradiation or were newly diagnosed and who refused surgery or were not surgical candidate.
- The primary endpoint was the proportion of patients who achieved normal (UFC) levels at the end of the randomized withdrawal period, without the need for uptitration.
- Results showed that osilodrostat improves the proportion of patients who achieve a normal UFC level compared to placebo. However, additional study is warranted as study was relatively short term and used a different dosing schedule than the FDA approved, recommend dose.

Recorlev (levoketoconazole) for Endogenous Cushing's Syndrome (CS)[21 22]

- The safety and efficacy of Recorlev (levoketoconazole) was evaluated in two phase 3 trials (SONICS and LOGICS) in adults with endogenous CS.
    * All patients in both studies had endogenous CS with a mUFC>1.5x the upper limit of normal and were either not eligible for surgery or had persistent/recurrent disease despite previous surgery.
    * Patients with pseudo or cyclic CS as well as endogenous CS due to either pituitary or adrenal carcinoma were excluded from trial.
    * SONICS (n=94) was a phase 3, open-label, single arm trial in adults consisting of a dose-titration phase, maintenance phase, and extended maintenance phase.
        - The dose was titrated based on mUFC response and patient tolerance, with the dose being established once mUFC was either less than upper limit of normal, max dose was obtained, or clinically meaningful response reached in the opinion of the investigator.
        - Once the therapeutic dose was achieved, the patients entered the maintenance phase of the trial, in which the primary endpoint was the number of patients to maintain mUFC normalization after 6 months without a dose increase.
        - Approximately 31% (n=29) met the primary endpoint of mUFC normalization after 6 months, with only 16 (17%) of patients still meeting that endpoint after the extended maintenance phase.
    * LOGICS (n=84) was a phase 3, open-label dose titration, with a randomized double-blind, placebo controlled, withdrawal and dose restoration phase.
        - Dose titration was similar to the SONICS trial, however they had to be on stable dose for 4 weeks prior to entry into randomized portion of trial.
        - 44 patients (22 in placebo and 22 in treatment arm) were enrolled in the randomized withdrawal phase of the trial in which the primary endpoint was loss of therapeutic response upon withdrawing to placebo vs those

with loss of response on levoketoconazole. Loss of response was defined as mUFC > than 1.5x the upper limit of normal or mUFC > 40% from baseline of withdrawal phase.
        - Significantly more patients in the placebo arm (96%, n=21), lost a response compared to 41% (n=9) of the patients in the levoketoconazole arm.
    * Results of both trials showed that levoketoconazole improved the number of patients achieving a normalized mUFC alone as well as when compared to placebo in a withdrawal trial.
    * However, there is low-quality evidence that Recorlev (levoketoconazole) has any clinically relevant effect on the long-term consequences of CS, including cardiovascular outcomes, bone loss, or death.
    * The evidence of efficacy for Recorlev (levoketoconazole) in CS is of poor quality because it is based on one small open label, single arm trial, and a small, randomized, placebo controlled, withdrawal trial with no active comparator.
- Use of ketoconazole (generic) is currently recommended by the Endocrine Society as well as the Pituitary Society as a second line option after surgical intervention fails or is not an option. [23] There is no trial evidence directly comparing the efficacy or safety of Recorlev (levoketoconazole) to ketoconazole (generic) in CS. The known adverse event profile of Recorlev (levoketoconazole) is similar to ketoconazole; therefore, the use of Recorlev (levoketoconazole) in patients who are intolerant to, or have a contraindication to, ketoconazole is considered not medically necessary and not coverable.

Guidelines:
- First-line mainstay treatment for Cushing's Syndrome (CS) is surgical resection of the tumor. If surgery is unsuccessful or not an option, pharmacologic treatment is considered second-line therapy.
- Pharmacologic options for treatment include the following with selection being individualized based on each patient's clinical scenario, severity of disease, availability and cost:
    * Steroidogenesis inhibitors: ketoconazole, metyrapone, mitotane, etomidate, Isturisa (osilodrostat).
    * Somatostatin analogues: cabergoline, Signifor (pasireotide).
    * Glucocorticoid-receptor antagonists: mifepristone.

CARCINOID SYNDROME - SYMPTOMATIC CONTROL IN CARCINOID (NET) TUMORS or VIPomas [1 14]
- The NCCN Neuroendocrine and Adrenal Tumors guideline list Sandostatin LAR Depot (octreotide LAR) and lanreotide (generic, Somatuline Depot) as category 2A recommendations for carcinoid syndrome.
- A 6-month, double-blind trial of malignant carcinoid syndrome evaluated the efficacy of Sandostatin LAR Depot (octreotide LAR) 10 mg, 20 mg, or 30 mg.

* Overall, mean daily stool frequency was decreased with Sandostatin LAR Depot (octreotide LAR). The average number of daily stools decreased from ~4.5 stools per day at baseline to ~2.5 stools per day.
* Mean daily flushing episodes also decreased with Sandostatin LAR Depot (octreotide LAR). The average number of daily flushing episodes decreased from 3.0-6.1 episodes per day at baseline to 0.6-1.0 episodes per day.
* The reductions observed with Sandostatin LAR Depot (octreotide LAR) are within the range reported in the published literature for patients treated with octreotide (generic) subcutaneous injection.

USE OF SANDOSTATIN LAR DEPOT (OCTREOTIDE LAR) IN OTHER CONDITIONS

- Use of non-long-acting octreotide (generic) is a standard of care treatment option for various secretory conditions, including but not limited to secretory diarrhea, chemotherapy-induced diarrhea, and gastrointestinal bleeding.
- However, there is insufficient evidence to establish Sandostatin LAR Depot (octreotide LAR) is superior to use of lower-cost octreotide (generic). Therefore, Sandostatin LAR Depot (octreotide LAR) is coverable only for the diagnoses listed in the policy (when the coverage criteria are met).
- There is interest in the use of long acting Sandostatin LAR (octreotide LAR) in chemotherapy-induced diarrhea, however, evidence is lacking (including two phase 3 trials failing) to establish Sandostatin LAR Depot (octreotide LAR) is superior to other standards of care (which includes lower cost octreotide (generic) or placebo in chemotherapy induced diarrhea, therefore use of Sandostatin LAR Depot (octreotide LAR) in this indication is considered " Not medically necessary".[24 25]
- Of note: as of the publication of this policy, octreotide (generic) does not have a medication coverage policy.

Safety [8 9 16 18 26]

- Pituitary disorder therapies may increase blood glucose levels or increase glucose tolerance. In patients with diabetes, blood glucose levels should be monitored, and anti-diabetic medications should be optimized prior to starting therapy.
- Signifor LAR (pasireotide LAR) was associated with higher rates of hyperglycemia (29% vs. 8%), diabetes mellitus (19% vs. 4%), and increased HbA1c (6% vs 2%) compared to Sandostatin LAR Depot (octreotide LAR). [10] Similar differences were observed when comparing Signifor LAR (pasireotide LAR) with lanreotide (generic, Somatuline Depot).
- Pasireotide (Signifor, Signifor LAR) is not recommended in patients with severe liver impairment.
- Baseline liver function tests [e.g., alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), and alkaline phosphatase (ALP)] should be less than 3 times the upper limit of normal before starting Somavert (pegvisomant).
- Similar to ketoconazole, Recorlev (levoketoconazole) has a boxed warning for hepatoxicity and QT interval prolongation. Use in patients with severe liver disease or taking

concurrent medications associated with QT prolongation is not recommended. Baseline liver and ECG should be obtained before starting Recorlev (levoketoconazole) as well as monitored frequently.

Dosing

Table 2: Recommended Dosing and Administration for Pituitary Disorder Therapies

Drug	Dosing Schedule

Lanreotide (generic, Somatuline Depot) [4]
 	
Administered by a trained health care professional
	- Acromegaly: 90 mg subcutaneously once every 4 weeks.
	  * After 3 months of treatment, the dose of lanreotide (generic, Somatuline Depot) may be adjusted based on GH and IGF-1 levels.
	  * The dosage range is lanreotide (generic, Somatuline Depot) 60 mg to 120 mg.
	  * Patients who are controlled on lanreotide (generic, Somatuline Depot) 60 mg or 90 mg every 4 weeks may be considered for an extended dosing interval of lanreotide (generic, Somatuline Depot) 120 mg every 6 or 8 weeks.
	- GEP-NET: 120 mg subcutaneously once every 4 weeks.
	- Treatment of adults with carcinoid syndrome: 120 mg subcutaneously once every 4 weeks.

Recorlev (levoketoconazole) [26]	- Endogenous Cushing's Syndrome:
	  * Initiate dosage at 150 mg orally twice daily.
	  * Titrate dosage by 150 mg daily no more frequently than every 2-3 weeks based on 24-hour urinary free cortisol levels and tolerability.
	  * The maximum recommended dose is 600 mg twice daily.

Mycapssa (octreotide) [2]	- Acromegaly:
	  * 40 mg orally daily, administered as 20 mg twice daily.
	  * The dose may be adjusted based on GH and IGF-1 levels.
	  * The maximum dose is 80 mg daily.

Sandostatin LAR Depot (octreotide LAR) [1]
 	
Administered by a trained health care professional
	- Acromegaly:
	  * 20 mg intramuscularly once every 4 weeks.
	  * The recommended dosage range is 10 mg to 40 mg every 4 weeks.
	  * After 3 months of treatment, the dose may be adjusted based on GH and IGF-1 levels.
	- Diarrhea associated with carcinoid tumors or VIPomas:
	  * 20 mg intramuscularly once every 4 weeks.
	  * The recommended dosage range is 10 mg to 40 mg every 4 weeks.
	  * After 2 months of treatment, the dose may be adjusted based on symptomatic control.
	- GEP-NETs: Up to 40 mg intramuscularly once every 4 weeks.
	- For patients with GEP NETS, carcinoid tumors, or VIPomas, the dose may be further increased as needed based on symptom control. Short acting octreotide may also be added to Sandostatin LAR Depot (octreotide LAR) for rapid relief of symptoms or breakthrough symptoms. [14]

Drug	Dosing Schedule
Signifor (pasireotide) [16] *Self-administered*	- Starting dose for acromegaly: 0.6 or 0.9 mg subcutaneously twice a day. - The dose of Signifor (pasireotide) should be adjusted based on response and tolerability. - The dosage range of Signifor (pasireotide) is 0.3 to 0.9 mg twice daily. - Prior to initiating Signifor (pasireotide) therapy, it is recommended that the following baseline evaluations are obtained: fasting plasma glucose, hemoglobin A1c, liver tests, serum potassium and magnesium, an electrocardiogram, and a gallbladder ultrasound.

Signifor LAR (pasireotide LAR) [18]
 	
Administered by a trained health care professional
	- Acromegaly: 40 mg intramuscularly once every 4 weeks.
	  * The dose of Signifor LAR (pasireotide LAR) may be increased to a maximum of 60 mg once every 4 weeks in patients who do not have normalized GH or IGF-1 levels after 3 months of treatment or decreased to 20 mg once every 4 weeks based on tolerability.
	  * Prior to initiating Signifor LAR (pasireotide LAR) therapy, it is recommended that the following baseline evaluations are obtained: fasting plasma glucose, hemoglobin A1c, liver tests, serum potassium and magnesium, and an electrocardiogram.
	- Cushing's disease: 10 mg intramuscularly once every 4 weeks.
	  * Based on FDA label, the dose of Signifor LAR (pasireotide LAR) may be increased following 4 months of treatment in patients who have not normalized 24-hour urinary free cortisol (UFC). Based on tolerability, the dose may be increased to a maximum of 40 mg once every 4 weeks.
	  * Prior to initiating Signifor LAR (pasireotide LAR) therapy, it is recommended that the following baseline evaluations are obtained: fasting plasma glucose, hemoglobin A1c, liver tests, serum potassium and magnesium, and an electrocardiogram.

Somavert (pegvisomant) [9] *Self-administered*	- Loading dose: 40 mg subcutaneously done under physician supervision. - Somavert (pegvisomant) 10 mg subcutaneously once daily. - The daily dose of Somavert (pegvisomant) should be adjusted in 5 mg increments until serum IGF-I concentrations are maintained within normal range. IGF-I levels should be measured every 4 to 6 weeks. Doses should not be adjusted based on GH levels or signs/symptoms of acromegaly. - The dosage range of Somavert (pegvisomant) is 10 mg to 30 mg daily. - Prior to initiating Somavert (pegvisomant) therapy, it is recommended that baseline liver function tests are obtained. If AST or ALT is greater than 3 times the upper limit of normal, a work-up should be performed prior to Somavert (pegvisomant) administration.

Appendix 1: Lower-Cost Medications Used in the Management of Cushing's Disease [23 26 27]
Cabergoline (generic)
Ketoconazole (generic)
Metyrapone (Metopirone)
Mitotane (Lysodren)

Appendix 2: Endogenous Cushing's Syndrome Etiologies indicated for Recorlev use.[21 22]
Cushing's Disease (Pituitary adenoma)
Ectopic adrenocorticoticotrophic hormone (ACTH) secreting tumor
Adrenal adenoma
Adrenal hyperplasia

Codes	Number	Description
HCPCS	J1930	Injection, lanreotide (Somatuline Depot), 1 mg
HCPCS	J1932	Injection, lanreotide (Cipla), 1 mg
HCPCS	J2502	Injection, pasireotide long acting (Signifor LAR), 1 mg
HCPCS	J2353	Injection, octreotide, depot form for intramuscular injection (Sandostatin LAR Depot), 1 mg

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Revision History

Revision Date	Revision Summary
9/19/2024	• No criteria changes with this annual review.
9/14/2023	• Added use of Sandostatin LAR (octreotide LAR) as "Not medically necessary" for use in chemotherapy induced diarrhea.
9/23/2022	• Added coverage for Recorlev (levoketoconazole), a new medication for endogenous Cushing's syndrome (CS). • Added lanreotide, a new generic product for Somatuline Depot. • Clarified intent of step therapy for Cushing's Disease (lower-cost medication treatment option); associated appendix updated. • Removed step through Sandostatin LAR Depot (octreotide LAR) in acromegaly for pediatric patients. • Simplified initial authorization quantity limits on Sandostatin LAR Depot (octreotide LAR).
10/15/2021	• Clarified authorization periods and quantity limits. • Updated preferred long-acting somatostatin analog for carcinoid syndrome and GEP-NETs.
10/28/2020	• Added Sandostatin LAR Depot (octreotide LAR) to policy and archived standalone octreotide policy (formerly dru489). • Added Mycapssa (octreotide) delayed release capsules as a new medication for acromegaly. • Added Isturisa (osilodrostat) as a new medication for Cushing's Disease. • Added continuation of therapy (COT) criteria to policy. No change to intent of policy. • Clarified that the dose of Sandostatin LAR Depot (octreotide LAR) may be increased to greater than 40 mg every 4 weeks in patients who have continue to have symptoms on standard and require additional symptom control.
10/23/2019	Clarification of policy criteria wording, for operational clarity (no change to coverage intent with this annual update).
10/19/2018	Added coverage of Signifor LAR (pasireotide LAR) for Cushing's disease consistent with its new FDA-approved indication.
10/13/2017	Added coverage of Somatuline Depot for carcinoid syndrome in adults consistent with its new FDA-approved indication.
2/17/2017	New policy (effective 7/1/17).

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Medication Policy Manual | **Policy No:** dru489

Topic: Sandostatin LAR Depot, octreotide long-acting release | **Date of Origin:** June 1, 2017

Committee Approval Date: October 23, 2019 | **Next Review Date:** October 2020

Effective Date: January 1, 2020

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Octreotide long-acting release (Sandostatin LAR Depot) is a somatostatin analog indicated for acromegaly, diarrhea or flushing associated with metastatic carcinoid tumors, and watery diarrhea associated with vasoactive intestinal peptide tumors (VIPomas). The long-acting release (LAR) formulation is given intramuscularly once every four weeks.

This policy and the coverage criteria below do not apply to octreotide (generic). Octreotide (generic) does not require pre-authorization.

Policy/Criteria

I. Most contracts require pre-authorization approval of octreotide LAR (Sandostatin LAR Depot) prior to coverage. Octreotide LAR (Sandostatin LAR Depot) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) of use for one of the following indications, as listed in criteria A, B, or C below.

A. Unresectable, locally advanced or metastatic **gastroenteropancreatic neuroendocrine tumors (GEP-NETs)** [e.g. gastrointestinal tract, lung, thymus, or pancreatic neuroendocrine tumors].

OR

B. **Carcinoid tumors** (metastatic) OR **vasoactive intestinal peptide tumors (VIPomas),** with documented associated severe diarrhea and/or flushing episodes

OR

C. **Acromegaly**

II. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services does not consider octreotide LAR (Sandostatin LAR Depot) to be a self-administered medication.

B. When pre-authorization is approved, octreotide LAR (Sandostatin LAR Depot) may be authorized in the following quantities:

1. **Carcinoid tumors, VIPomas, or GEP-NET**

a. **Initial authorization:** Up to #1 octreotide LAR (Sandostatin LAR Depot) 20-mg kit every 4 weeks for 2 months.

b. **Continued authorization:** Up to #1 octreotide LAR (Sandostatin LAR Depot) 40 mg every 4 weeks.

2. **Acromegaly**

a. **Initial authorization:** Up to #1 octreotide LAR (Sandostatin LAR Depot) 20-mg kit every 4 weeks for 3 months.

b. **Continued authorization:** Up to #1 octreotide LAR (Sandostatin LAR Depot) 40 mg every 4 weeks.

C. Authorization may be reviewed annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

III. Octreotide LAR (Sandostatin LAR Depot) is considered investigational when used for all other conditions, including meningiomas, portal hypertension, and other cancer settings.

Position Statement

Summary

- Somatostatin is a natural hormone that lowers excessive growth hormone (GH) levels. Somatostatin analogs, such as octreotide LAR (Sandostatin LAR Depot), work by binding to somatostatin receptors, thereby suppressing GH secretion. They also inhibit adrenocorticotropic hormone (ACTH) secretion, which leads to decreased cortisol secretion.
- The intent of this policy is to allow for coverage of octreotide LAR (Sandostatin LAR Depot) for the indications where is has been shown to be safe and effective, including both FDA indications (as detailed in the coverage criteria) and those uses supported in standard of care guidelines (GEP-NET), for up to the doses supported in clinical trials.
    * Somatostatin analogs, such as octreotide (generic, Sandostatin LAR Depot), is FDA-approved for treatment of acromegaly.
    * Octreotide LAR (Sandostatin LAR Depot) is also FDA-approved for severe diarrhea and flushing episodes associated with metastatic carcinoid tumors, and profuse watery diarrhea associated with vasoactive intestinal peptide-secreting tumors (VIPomas).
    * Octreotide LAR (Sandostatin LAR Depot) is not FDA-approved for locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors GEP-NET; however, its use is supported by clinical trials, as well as standard of care guidelines [National Comprehensive Cancer Network (NCCN)].
- The recommended initial dosing for octreotide LAR (Sandostatin LAR Depot) for acromegaly or for symptomatic control in carcinoid tumors or VIPomas is 20 mg intramuscular injection given by a health care provider once every 4 weeks. Dosing adjustments should be made after two or three months, based on response and tolerability, up to a maximum dose of 40 mg every 4 weeks for acromegaly and 30 mg every 4 weeks for carcinoid tumors or VIPomas. Although the use of octreotide LAR (Sandostatin LAR Depot) for GEP-NET is not a FDA-approved use, the dose of 20 mg per month is a suggested starting dose per guidelines and expert input, to prevent excessive dosing and associated adverse events.
- The safety and efficacy of doses exceeding the maximum dosage in the FDA-approved labeling have not been established in clinical trials; however, the NCCN guidelines suggest higher doses may be of value in GEP-NET or VIPoma and carcinoid syndrome when starting doses are insufficient for disease control, as detailed in the coverage criteria.

Clinical Efficacy

ACROMEGALY

- A single, high quality meta-analysis found that in patients taking octreotide LAR (Sandostatin LAR Depot) who were not preselected for somatostatin analog responsiveness, 54% met GH efficacy criteria and 63% had IGF-I normalization. [2]
- A single, low quality meta-analysis evaluated head-to-head studies between octreotide LAR (Sandostatin LAR Depot) and lanreotide (Somatuline Depot). [3]
    * A GH level < 2.5 µg/L was achieved in 65.3% of patients on octreotide LAR (Sandostatin LAR Depot) versus 59.5% of patients on lanreotide (Somatuline Depot).
    * Normalization of IGF-I was achieved in 46.7% of patients on octreotide LAR (Sandostatin LAR Depot) versus 52.7% of patients on lanreotide (Somatuline Depot).
    * Biochemical control was achieved in 46% of patients on octreotide LAR (Sandostatin LAR Depot) versus 41.9% of patients on lanreotide (Somatuline Depot).
- The Endocrine Society clinical guidelines for acromegaly recommend transsphenoidal surgery as first-line treatment for most patients. [1]
    * Pharmacological treatment with a somatostatin analog or pegvisomant (Somavert) is recommended as the initial adjuvant medical therapy.
    * In patients with mild disease, a trial of a dopamine agonist, such as cabergoline, is recommended as the initial adjuvant medical therapy.
    * Patients with an inadequate response to a somatostatin analog should try adding cabergoline or pegvisomant (Somavert).

SYMPTOMATIC CONTROL IN CARCINOID (NET) TUMORS or VIPomas

- A 6-month, double-blind trial of malignant carcinoid syndrome evaluated the efficacy of octreotide LAR (Sandostatin LAR Depot) 10 mg, 20 mg, or 30 mg. [4]
    * Overall, mean daily stool frequency was decreased with octreotide LAR (Sandostatin LAR Depot). The average number of daily stools decreased from ~4.5 stools per day at baseline to ~2.5 stools per day.
    * Mean daily flushing episodes also decreased with octreotide LAR (Sandostatin LAR Depot). The average number of daily flushing episodes decreased from 3.0-6.1 episodes per day at baseline to 0.6-1.0 episodes per day.
    * The reductions observed with octreotide LAR (Sandostatin LAR Depot) are within the range reported in the published literature for patients treated with octreotide (generic) subcutaneous injection.

GASTROENTEROPANCREATIC NEUROENDOCRINE TUMORS (GEP-NETs)

- The PROMID trial showed an improvement in time to tumor progression in neuroendocrine tumors of the midgut with octreotide LAR (Sandostatin LAR Depot) compared to placebo (14.3 months vs. 6 months). [5]

- The National Comprehensive Cancer Network (NCCN) Neuroendocrine Tumors guideline list octreotide LAR (Sandostatin LAR Depot) as category 2A recommendation for gastrointestinal tract, lung, thymus, or pancreatic neuroendocrine tumors (GEP-NET). [6]
- A single systematic review showed that dose escalation up to 120 mg every 4 weeks may be considered for symptom control and tumor progression in neuroendocrine tumors; however, there was a lack of quantitative measurements of symptom severity and mainly supported by expert opinion. [6]
- Additional prospective randomized controlled studies are needed to establish the safety and efficacy of above label dosing for octreotide LAR (Sandostatin LAR Depot).

Investigational Uses

- Although there is interest in using octreotide LAR (Sandostatin LAR Depot) in a variety of other cancer settings (not listed above), there is currently no published randomized trials to support the efficacy and safety of octreotide LAR (Sandostatin LAR Depot) in these settings.
- The safety and efficacy of octreotide LAR (Sandostatin LAR Depot) has not been established in portal hypertension. [7]
- The dose escalation of octreotide LAR (Sandostatin LAR) in excess of 30 mg every 4 weeks in the treatment of carcinoid tumors or GEP-NET for somatostatin analogue resistance is considered investigational. While trials of telotristat (Xermelo) included a significant portion of patients who used octreotide LAR (Sandostatin LAR) in excess of 30 mg per 4 weeks, there is insufficient evidence to establish any benefit from dosing in excess of 30 mg every 4 weeks. As such, the use is considered investigational and cannot be covered. [8]

Safety [4]

- The most common adverse reactions associated with octreotide LAR (Somatostatin LAR Depot) in acromegaly were diarrhea, cholelithiasis, abdominal pain, and flatulence.
- The most common adverse reactions associated with octreotide LAR (Somatostatin LAR Depot) in carcinoid tumors and VIPomas were back pain, fatigue, headache, abdominal pain, nausea, and dizziness.
- Similarly to other somatostatin analogs, when octreotide LAR (Somatostatin LAR Depot) treatment is initiated, blood glucose levels should be monitored and anti-diabetic therapies should be adjusted accordingly.

Dosing

- Patients should be maintained on octreotide (generic) subcutaneous injection for at least 2 weeks to determine tolerance prior to initiating octreotide LAR (Sandostatin LAR Depot).
- The recommended dosing for octreotide LAR (Sandostatin LAR Depot) in acromegaly is as follows: [4]
    * Octreotide LAR (Sandostatin LAR Depot) 20 mg intramuscularly once every 4 weeks.

    * After 3 months of treatment, the dose of octreotide LAR (Sandostatin LAR Depot) may be adjusted based on GH and IGF-1 levels.
    * The recommended dosage range is octreotide LAR (Sandostatin LAR Depot) 10 mg to 40 mg.
- The recommended dosing for octreotide LAR (Sandostatin LAR Depot) in diarrhea associated with carcinoid tumors or VIPomas is as follows: [4]
    * Octreotide LAR (Sandostatin LAR Depot) 20 mg intramuscularly once every 4 weeks.
    * After 2 months of treatment, the dose of octreotide LAR (Sandostatin LAR Depot) may be adjusted based on symptomatic control.
    * The recommended dosage range is octreotide LAR (Sandostatin LAR Depot) 10 mg to 30 mg.
- The recommended dosing for octreotide LAR (Sandostatin LAR Depot) in GEP-NETs is 20 mg to 30 mg intramuscularly once every 4 weeks. [6]
- Octreotide LAR (Sandostatin LAR Depot) should be administered by a trained health care professional.

Cross References
Pituitary Disorder Therapies, Medication Policy Manual, Policy No. dru488

Codes	**Number**	**Description**
HCPCS	J2353	Injection, octreotide, depot form for intramuscular injection, 1 mg

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Revision History

Revision Date	Revision Summary
10/23/2019	- Clarification of policy criteria wording, for operational clarity (no change to coverage intent with this annual update). - Update quantity limit for GEP-NET.
10/19/2018	Simplification of coverage criteria (remove step therapy with octreotide immediate-release) and removal of thymic malignancy as an Investigational Use.
10/13/2017	Clarification of covered diagnoses. No changes to coverage criteria with this annual update.
02/17/2017	New policy (effective 7/1/17)

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Medication Policy Manual | **Policy No:** dru499

Topic: Bavencio, avelumab | **Date of Origin:** July 14, 2017

Committee Approval Date: September 19, 2024 | **Next Review Date:** 2025

Effective Date: January 1, 2025

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Bavencio (avelumab) is an intravenously administered immunotherapy used in the management of certain types of cancer. It belongs to a class of medications called programmed death-ligand (PD-L1) blocking antibodies.

Policy/Criteria

Most contracts require pre-authorization approval of Bavencio (avelumab) prior to coverage.

I. Continuation of therapy (COT): Bavencio (avelumab) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Bavencio (avelumab) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criterion A, B, or C below is met.

A. A diagnosis of **Merkel cell carcinoma**, metastatic, when criteria 1 and 2 below are met:

1. Bavencio (avelumab) will be used as monotherapy.

AND

2. No prior use of programmed death receptor-1 blocking antibody therapy (PD-1 inhibitors) or programmed death-ligand 1 blocking antibody therapy (PD-L1 inhibitors) [see *Appendix 1*].

OR

B. A diagnosis of **urothelial carcinoma** (bladder cancer), locally advanced or metastatic, when criteria 1, 2, and 3 below are met:

1. Prior treatment with platinum-containing chemotherapy.

AND

2. Bavencio (avelumab) will be used as monotherapy.

AND

3. No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

OR

C. A diagnosis of **renal cell carcinoma** (RCC), recurrent or metastatic, when criteria 1 through 4 below are met:

1. The tumor has clear cell histology.

AND

2. There has been no prior systemic therapy for advanced disease.

AND

3. Bavencio (avelumab) will be administered in combination with Inlyta (axitinib).

AND

4. No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy services considers Bavencio (avelumab) coverable only under the medical benefit (as a provider- administered medication).

B. When pre-authorization is approved, Bavencio (avelumab) will be authorized for 24 weeks in quantities of up to 800 mg every 2 weeks, until disease progression.

C. Reauthorization: Authorization **shall** be reviewed at least every 24 weeks for documented benefit. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met. Specifically, documentation that the medication is providing clinical benefit, including disease stability or improvement, and lack of disease progression, based on an assessment of change in tumor burden. If there is documentation of potential disease progression, a shortened authorization (up to three months) may be approved to allow time for clarification of response to Bavencio (avelumab), including clinical re-evaluation of the patient and reimaging.

PLEASE NOTE: Additional doses of Bavencio (avelumab) will not be authorized without a documented recent assessment by the treating provider (such as oncologist) with objective evidence of response to therapy, such as by re-imaging and use of iRECIST criteria.

IV. Bavencio (avelumab) is considered investigational when used for all other conditions, including but not limited to:

A. Gastric or gastroesophageal junction (GEJ) adenocarcinoma

B. Non-small cell lung cancer (NSCLC)

C. Renal cell carcinoma (RCC), when used in the subsequent-line treatment setting.

Position Statement

Summary

- Bavencio (avelumab) is a programmed death-ligand 1 (PD-L1) blocking antibody (immunotherapy) used in the treatment of several types of cancer.
- The intent of this policy is to cover Bavencio (avelumab) in settings where it has been studied and shown to be safe and effective, as detailed in the coverage criteria, with consideration for other available treatment options.
    * Where there is lack of proven additional benefit and/or lack of demonstrated health outcome (such as overall survival or improved quality of life) relative to alternative therapies, use of Bavencio (avelumab) alone or in combination with other therapies is not coverable ("not medically necessary" or "investigational").
    * It is important to note that the fact that a medication is FDA approved for a specific indication does not, in itself, make the treatment medically reasonable and necessary.
- Many of the clinical indications for immunotherapies (PD-1, PD-L1, and others) have been approved by the FDA and endorsed by clinical guidelines based on surrogate measures such as overall tumor response rate (ORR) and progression-free survival (PFS) which are not proven to accurately predict clinically important outcomes such as improved overall survival or improved quality of life.
- National Comprehensive Cancer Network (NCCN) guidelines recommend Bavencio (avelumab) as a potential option in each of the treatment settings listed in the coverage criteria. In general, NCCN recommendations parallel the FDA approved indications.
- The PD-1 and PD-L1 inhibitors have the potential to cause immune-mediated adverse reactions that can result in pneumonitis, colitis, hepatitis, endocrinopathies, and nephritis.
- Bavencio (avelumab) is intravenously administered in a dose of 800 mg every two weeks, until disease progression.
- Optimal sequencing of chemotherapy and immunotherapy in many cancers is unknown or the data is evolving. At this time, sequential use of immunotherapies is not supported by current evidence. Specifically, there is no evidence to support the sequential use of different PD-1 or PD-L1 inhibitors once there is disease progression on prior PD-1 or PD-L1 inhibitor therapy, as well as use of adjuvant PD-1/PD-L1 inhibitor after neoadjuvant PD-1/PD-L1 inhibitor therapy (unless explicitly listed in the coverage criteria). Therefore, the use of sequential courses of PD-1/PD-L1 immunotherapy is not coverable.
- There are ongoing studies using Bavencio (avelumab) in a variety of other cancers. However, although initial evidence may be promising, the potential for clinical benefit in these conditions is still being investigated.
- *Reauthorization Criteria*: When coverage criteria are met, Bavencio (avelumab) is authorized for six months (24 weeks) of therapy, after which time documentation must be provided to establish that the medication is effective. Specifically, there must be documentation of clinical benefit, including disease stability or improvement and there is a lack of disease progression, based on an assessment of change in tumor burden.
    * The standard of care for evaluation of response to cancer immunotherapy, such as Bavencio (avelumab) is use of the iRECIST criteria for assessment of tumor burden. [1]

* The iRECIST criteria include use of quantitative and qualitative criteria for assessment of change in tumor burden for target lesions and non-target lesions. [2]
    - Quantitative measurements for target lesions (tumor size and % change)
    - Qualitative evaluation for non-target lesions (present/disappeared/ unequivocal progression)
* Documentation of benefit must include an assessment of the most recent imaging ("restaging scans") by the treating oncologist. Given the complexity of the evaluation, including use of the iRECIST criteria, Bavencio (avelumab) will not be reauthorized without an assessment of response to therapy, such a partial response (iPR), complete response (iCR), or stable disease (iSD).
* Use of immunotherapy may result in pseudoprogression, due to immune and T-cell activation, which can appear similar to tumor flare. If there is documentation of potential disease progression ["unconfirmed progressive disease (iUPD)"], a shortened authorization (up to three months) may be approved to allow time for clarification of response to Bavencio (avelumab), including clinical re-evaluation of the patient and reimaging. Guidelines recommend reimaging for iUPD after 4-8 weeks.
* If a patient has confirmed, unequivocal new lesions (progression of disease, iPD), additional Bavencio (avelumab) is not coverable. If a new lesion is equivocal, iUPD reassessment by the treating oncologist with repeat imaging would apply (as noted above).

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy

MERKEL CELL CARCINOMA (MCC) [3 4]

- Bavencio (avelumab) is approved for the treatment of metastatic MCC, regardless of prior therapy.
- Initial FDA approval of Bavencio (avelumab) in MCC was based on results from a single-group, open-label (observational) trial that evaluated it in patients with stage IV (metastatic) MCC that had progressed after cytotoxic chemotherapy.
    * All subjects in the study had progressed on at least one prior line of chemotherapy in the metastatic setting.
    * The study reported overall tumor response rate (ORR) as the primary endpoint. The clinical meaningfulness of this endpoint is unclear, as it has not been shown to accurately predict any clinically relevant outcome.
    * An overall ORR of 33% was reported in the trial. The duration of response ranged from 2.8 months to upwards of 23 months.
- Approval in treatment-naïve MCC patients was extrapolated from this initial study. However, there is now an ongoing study prospectively evaluating Bavencio (avelumab) in the front-line MCC setting.
- The relative safety and effectiveness of Bavencio (avelumab) in MCC is unknown as it has not been compared with either best supportive care, or with any other therapy. Chemotherapy historically has been the standard approach for advanced MCC. Although MCC appears to be chemosensitive, the duration of response is limited. The impact of chemotherapy on survival in patients with metastatic MCC is unclear.[5]

UROTHELIAL CANCER (BLADDER CANCER)

- Bavencio (avelumab) is approved in two bladder cancer settings: [6]
    * As a subsequent-line therapy when there has been progression of locally advanced or metastatic disease after front-line platinum-containing chemotherapy.
    * As switch maintenance when there has been no progression of disease after front-line platinum-containing chemotherapy.
- The initial FDA approval for Bavencio (avelumab) in bladder cancer was based on a phase 1, non-blinded, single-arm cohort from a larger study in a variety of solid tumors. [7 8]
    * The study evaluated ORR as the primary endpoint. ORR is not a validated surrogate endpoint. It has not been shown to accurately predict any clinically relevant benefit in locally advanced or metastatic bladder cancer.
    * The reported ORR was 14.8% and the duration of response was not estimable.
- To date, Bavencio (avelumab) has only been studied after platinum-based therapy.
- More recently, avelumab (Bavencio) was approved as switch maintenance therapy for locally advanced or metastatic bladder cancer after successful treatment with platinum-containing chemotherapy [JAVELIN Bladder 100 study]. [9]
    * Subjects in the trial were initially treated with four to six cycles of a platinum plus gemcitabine. If the tumor decreased in size or did not progress on the initial chemotherapy, subjects were given Bavencio (avelumab) or best supportive care until disease progression.

    * Subjects in the Bavencio (avelumab) treatment arm were noted to have improved survival relative to those who received best supportive care with a median OS of 21.4 months and 14.3 months, respectively.
- Platinum-based chemotherapy is the standard of care for front-line treatment of advanced or metastatic bladder cancer as it is associated with improved OS. Ideal sequencing of therapies in bladder cancer is still under investigation. Because only 43% of subjects in the chemotherapy only arm of the JAVELIN Bladder 100 study received a PD-1 or PD-L1 inhibitor after disease progression, it cannot be determined whether Bavencio (avelumab) maintenance is superior to waiting until disease progression before beginning anti-PD-1/PD-L1 therapy.
- The NCCN bladder cancer guideline lists several different anti-PD-1/PD-L1 medications, including Bavencio (avelumab), among its recommendations for bladder cancer in several different disease settings. [5]

RENAL CELL CARCINOMA (RCC)

- Bavencio (avelumab) is approved for the treatment of advanced (unresectable or metastatic) renal cell carcinoma (RCC) as a front-line therapy when used in combination with Inlyta (axitinib).
- The approval was based on interim results from a phase 3, open-label (not blinded), randomized controlled trial (RCT) in patients with advanced, clear cell RCC in the front-line treatment setting, comparing the combination of Bavencio (avelumab) plus Inlyta (axitinib) with sunitinib monotherapy [JAVELIN Renal 101 study]. [6 10] Sunitinib, like Inlyta (axitinib), is an orally administered tyrosine kinase inhibitor.
    * Median progression-free survival (PFS) was greater in the combination treatment arm [13.8 months and 8.4 months in the Bavencio (avelumab)/Inlyta (axitinib) and sunitinib treatment arms, respectively].
    * There was no difference in overall survival (OS) detected between groups at the time of the interim analysis. It is not known if Bavencio (avelumab)/Inlyta (axitinib) improves any clinical outcome at this time.
    * There was a slight increase in grade 3 and 4 adverse effects in the combination arm. Additionally, 11% of subjects in the combination arm had immune-mediated AEs that required 40 mg or more per day of prednisone.
- There is no evidence supporting the use of Bavencio (avelumab) in subsequent-line RCC settings, or as a monotherapy for RCC.
- The NCCN kidney cancer guideline lists the combination of Bavencio (avelumab) and axitinib (Inlyta) among several recommended regimens when used as a first-line treatment for advanced, clear cell RCC. [5]
- The ideal sequencing of immunotherapies [such as Bavencio (avelumab), Opdivo (nivolumab), Keytruda (pembrolizumab), and Yervoy (ipilimumab)] and tyrosine kinase inhibitor (TKI) therapies [Inlyta (axitinib), Cabometyx (cabozantinib), Lenvima (Lenvatinib), Votrient (pazopanib), and sunitinib] in advanced RCC has not been established. Further study is needed.

Investigational Uses

- Bavencio (avelumab) is actively being studied to determine if there is benefit in treating other types of cancers including gastric or gastroesophageal junction (GEJ)

adenocarcinoma (including esophageal) and NSCLC. [11] To date, there are no studies establishing a clinical benefit in these settings.

- There is an early phase, published study evaluating Bavencio (avelumab) in NSCLC. However, larger, well-controlled studies are necessary to establish the safety and effectiveness of Bavencio (avelumab) in this setting. [12]

Dosing [6]

- Bavencio (avelumab) is given as a 60-minute infusion in a dose of 800 mg every two weeks. It is continued until disease progression or unacceptable toxicity.
- In RCC, it is given in combination with axitinib (Inlyta) 5 mg orally twice daily.

Appendix 1: FDA-approved PD-1 and PD-L1 blocking monoclonal antibody therapies [a]
Programmed death receptor-1 (PD-1) inhibitors
Jemperli (dostarlimab)
Keytruda (pembrolizumab)
Libtayo (cemiplimab)
Loqtorzi (toripalimab)
Opdivo (nivolumab)
Tevimbra (tislelizumab)
Zynyz (retifanlimab)
Programmed death-ligand 1 (PD-L1) inhibitor
Bavencio (avelumab)
Imfinzi (durvalumab)
Tecentriq (atezolizumab)

[a] Or as listed on the FDA.gov website

Cross References
Inlyta, axitinib, Medication Policy Manual, Policy No. dru273
Keytruda, pembrolizumab, Medication Policy Manual, Policy No. dru367
Libtayo, cemiplimab, Medication Policy Manual, Policy No. dru565
Opdivo, nivolumab, Medication Policy Manual, Policy No. dru390
Yervoy, ipilimumab, Medication Policy Manual, Policy No. dru238
Zynyz, retifanlimab, Medication Policy Manual, Policy No. dru751

Codes	Number	Description
HCPCS	J9023	Injection, avelumab (Bavencio), 10 mg

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Revision History

Revision Date	Revision Summary
9/19/2024	**Effective 1/1/2025:** Changed reauthorization from 'may' to 'shall.' Operationally, all approvals will be for 24 weeks (6 months). Ongoing therapy (beyond 24 weeks) will be subject to reauthorization review every 24 weeks, for documentation of disease stability or improvement and lack of disease progression.
12/7/2023	No criteria changes with this annual review.
12/9/2022	• Updated standard language in policy. • No changes to coverage criteria with this annual update.
4/21/2021	• Simplified and broadened the bladder cancer criteria by replacing the prior list of covered treatment settings with 'Prior treatment with platinum-containing chemotherapy'. This change allows for use in the new switch maintenance setting as well as in subsequent-line treatment settings. • Under renal cell carcinoma (RCC) the requirement for 'clear cell' histology was moved from the disease description to a separate numbered criterion to make sure it is not missed when applying coverage criteria (no change to intent of original criteria). • COT language was updated (no change to intent of coverage criteria).
1/22/2020	Added continuation of therapy (COT) criteria (no change to intent of coverage criteria).
10/23/2019	No criteria changes with this annual update.
7/24/2019	Effective 8/15/2019: • Updated policy with criteria for coverage in front-line RCC, which is a new FDA-approved indication • Updated with standard policy language (does not change intent).
10/30/2018	Updated dosing to flat 800 mg dosing, to reflect FDA label change.
4/20/2018	No changes with this annual update. Clarified authorization is valid "until disease progression" (no change to intent).

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Medication Policy Manual | **Policy No:** dru500

Topic: Imfinzi, durvalumab | **Date of Origin:** September 8, 2017

Committee Approval Date: September 19, 2024 | **Next Review Date:** 2025

Effective Date: January 1, 2025

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Imfinzi (durvalumab) is an intravenously administered immunotherapy used in the treatment of several different cancers. It belongs to a class of medications called programmed death-ligand (PD-L1) blocking antibodies.

Policy/Criteria

Most contracts require pre-authorization approval of Imfinzi (durvalumab) prior to coverage.

I. Continuation of therapy (COT): Imfinzi (durvalumab) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Imfinzi (durvalumab) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criterion A, B, C, D, E, or F below is met.

A. A diagnosis of **non-small cell lung cancer (NSCLC), locally advanced (unresectable stage III),** when all criteria 1 through 4 below are met.

1. The patient has received 2 or more cycles of definitive concurrent platinum-containing chemotherapy and radiation therapy.

AND

2. There has been no disease progression during or following platinum-containing chemotherapy and radiation therapy.

AND

3. Imfinzi (durvalumab) is used as monotherapy.

AND

4. No prior use of programmed death receptor-1 blocking antibody therapy (PD-1 inhibitors) or programmed death-ligand 1 blocking antibody therapy (PD-L1 inhibitors) (see *Appendix 1*).

OR

B. A diagnosis of **metastatic non-small cell lung cancer (NSCLC)** when criteria 1 through 4 below are met:

1. There has been no prior systemic therapy for metastatic NSCLC.

AND

2. There are no sensitizing epidermal growth factor (EGFR) mutations or anaplastic lymphoma kinase (ALK) genomic tumor aberrations.

AND

3. Imfinzi (durvalumab) will be used in combination with Imjudo (tremelimumab) AND platin doublet chemotherapy.

AND

4. No prior use of PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

OR

C. A diagnosis of **small cell lung cancer, extensive-stage (ES-SCLC),** when criteria 1 through 3 below are met:

1. No prior systemic treatment for extensive stage SCLC (ES-SCLC) [not including any systemic treatment for early/limited-stage SCLC].

AND

2. Imfinzi (durvalumab) is initiated in combination with etoposide and either cisplatin or carboplatin.

AND

3. No prior use of PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

OR

D. A diagnosis of **biliary tract cancer (BTC), unresectable locally advanced or metastatic,** when criteria 1 through 3 below are met:

1. No prior systemic treatment in the advanced or metastatic disease setting.

AND

2. Imfinzi (durvalumab) will be used in combination with gemcitabine plus cisplatin.

AND

3. No prior use of PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

PLEASE NOTE: Biliary tract cancer includes intrahepatic cholangiocarcinoma (CCA), extrahepatic CCA, gallbladder cancer, and ampulla of Vater cancer.

OR

E. A diagnosis of **<u>unresectable</u> hepatocellular carcinoma (HCC)** when criteria 1 through 4 below are met:

1. There has been no prior systemic therapy for unresectable HCC.

AND

2. Patient has a Child-Pugh score of 5 to 6 (Class A). [provider attestation]

AND

3. Imfinzi (durvalumab) will be used in combination with Imjudo (tremelimumab).

AND

4. No prior use of PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

OR

F. A confirmed diagnosis of **endometrial carcinoma**, **unresectable locally advanced or metastatic**, when criteria 1 through 4 below are met:

1. No prior systemic therapy in the advanced disease setting.

AND

2. The tumor is mismatch repair deficient (dMMR).

AND

3. Imfinzi (durvalumab) will be initiated in combination with carboplatin and paclitaxel.

AND

4. No prior use of PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy services considers Imfinzi (durvalumab) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Imfinzi (durvalumab) will be authorized in quantities as follows for the following durations:

1. ***NSCLC, locally advanced (unresectable, Stage 3)*:** For 24 weeks, up to two, 10 mg/kg infusions every 28 days OR 1500 mg every 4 weeks until disease progression or for up to a maximum of 12 months.

2. ***NSCLC, metastatic (in combination with Imjudo):*** For 24 weeks, up to 1500 mg every 3 weeks for up to 4 cycles, then 1500 mg every 4 weeks until disease progression.

3. ***ES-SCLC*:** For 24 weeks, up to 1500 mg every 3 weeks for up to 6 cycles then 1500 mg every 4 weeks until disease progression.

4. ***BTC*:** For 24 weeks, up to 1500 mg every three weeks for up to 8 cycles then 1500 mg every 4 weeks until disease progression.

5. ***HCC:*** For 24 weeks, up to 1500 mg every four weeks until disease progression.

6. ***Endometrial carcinoma:*** For 24 weeks, up to 1,120 mg every 3 weeks for up to 6 cycles then 1,500 mg every four weeks until disease progression.

C. Reauthorization: Authorization **shall** be reviewed at least every 24 weeks for documented benefit. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met. Specifically, documentation that the medication is providing clinical benefit, including disease stability or improvement, and lack of disease progression, based on an assessment of change in tumor burden. If there is documentation of potential disease progression, a shortened authorization (up to three months) may be approved to allow time for clarification of response to Imfinzi (durvalumab), including clinical re-evaluation of the patient and reimaging.

PLEASE NOTE: Additional doses of Imfinzi (durvalumab) will not be authorized without a documented recent assessment by the treating provider (such as oncologist) with objective evidence of response to therapy, such as by re-imaging and use of iRECIST criteria.

IV. Imfinzi (durvalumab) is considered investigational when used for all other conditions, including but not limited to:

A. Non-small cell lung cancer (NSCLC) [other than specified in the criteria above].

B. Biliary tract cancer (BTC) in the second- and subsequent-line setting.

C. Cervical cancer.

D. Endometrial sarcoma.

E. Head and Neck cancer (HNSCC).

F. Urothelial carcinoma (bladder cancer).

Position Statement

Summary

- Imfinzi (durvalumab) is a programmed death-ligand (PD-L1) blocking antibody (immunotherapy) used in the treatment of several different cancers.
- The intent of this policy is to cover Imfinzi (durvalumab) in settings where it has been studied and shown to be safe and effective, as detailed in the coverage criteria, with consideration for other available treatment options.
    * Where there is lack of proven additional benefit and/or lack of demonstrated health outcome (such as overall survival or improved quality of life) relative to alternative therapies, use of Imfinzi (durvalumab) alone or in combination with other therapies is not coverable ("not medically necessary" or "investigational").
    * It is important to note that the fact that a medication is FDA approved for a specific indication does not, in itself, make the treatment medically reasonable and necessary.
- Many of the clinical indications for immunotherapies (PD-1, PD-L1, and others), including Imfinzi (durvalumab), have been approved by the FDA and endorsed by clinical guidelines based on surrogate measures such as overall tumor response rate (ORR) and progression-free survival (PFS) which are not proven to accurately predict clinically important outcomes such as improved overall survival or improved quality of life.
- More recently, Imfinzi (durvalumab) was shown to improve overall survival (OS) in several cancer settings when used in combination with other medications; however, the therapies to which it was compared did not always reflect current standards of care.
- National Comprehensive Cancer Network (NCCN) guidelines recommend Imfinzi (durvalumab) as a potential option in each of the treatment settings listed in the coverage criteria. In general, NCCN recommendations parallel the FDA approved indications.
- The PD-1 and PD-L1 inhibitors have the potential to cause immune-mediated adverse reactions that can result in pneumonitis, colitis, hepatitis, endocrinopathies, and nephritis.
- Imfinzi (durvalumab) is intravenously administered until disease progression, per the dosing limits in the coverage criteria.
- Optimal sequencing of chemotherapy and immunotherapy in many cancers is unknown or the data is evolving. At this time, sequential use of immunotherapies is not supported by current evidence. Specifically, there is no evidence to support the sequential use of different PD-1 or PD-L1 inhibitors once there is disease progression on prior PD-1 or PD-L1 inhibitor therapy, as well as use of adjuvant PD-1/PD-L1 inhibitor after neoadjuvant PD-1/PD-L1 inhibitor therapy (unless explicitly listed in the coverage criteria). Therefore, the use of sequential courses of PD-1/PD-L1 immunotherapy is not coverable.
- There are ongoing studies using Imfinzi (durvalumab) in a variety of other cancers. However, although initial evidence may be promising, the potential for clinical benefit in these conditions is still being investigated.
- The FDA indication for urothelial carcinoma (bladder cancer) was withdrawn after additional, confirmatory trials failed to demonstrate a health outcome for this indication. The use of Imfinzi (durvalumab) for bladder cancer is considered investigational.

- *Reauthorization Criteria*: When coverage criteria are met, Imfinzi (durvalumab) is authorized for six months (24 weeks) of therapy, after which time documentation must be provided to establish that the medication is effective. Specifically, there must be documentation of clinical benefit, including disease stability or improvement and there is a lack of disease progression, based on an assessment of change in tumor burden. Documentation of benefit must include an assessment of the most recent imaging ("restaging scans") and/or re-biopsy by the treating oncologist.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy

Non-Small Cell Lung Cancer (NSCLC)

Unresectable, stage III disease as maintenance:

- Imfinzi (durvalumab) was approved for use in unresectable, locally advanced (stage III) NSCLC that has not progressed after concurrent chemoradiation therapy. The FDA approval was based on one phase 3, randomized, double-blind, placebo-controlled trial that reported overall survival (OS) benefit at an interim analysis. [1]
    * Imfinzi (durvalumab) was given as monotherapy and was continued until disease progression (or until intolerable adverse effects) for a maximum of 12 months.
    * The 24-month overall survival rate was 66.3% (95% confidence interval [CI], 61.7 to 70.4) in the Imfinzi (durvalumab) group, compared with 55.6% (95% CI, 48.9 to 61.8) in the placebo group (p=0.005).

    * Median OS was not reached in the Imfinzi (durvalumab) group compared to 28.7 months in the placebo group (HR 0.68, 95% CI 0.53 to 0.87, p = 0.0025).
- It is unknown if there are any differences in safety or effectiveness relative to other therapies because the study did not employ any active comparators.
- Platinum-based chemotherapy is the standard of care for the first-line treatment of advanced NSCLC in tumors without driver mutations. However, the use of immuno-therapy is becoming quickly adopted as an alternative in many first and second-line metastatic NSCLC settings.
- The National Comprehensive Cancer Network (NCCN) NSCLC treatment guideline lists Imfinzi (durvalumab) as consolidation therapy when there is no progression after 2 or more cycles of definitive concurrent platinum-based chemoradiation. [2]

Metastatic disease setting:

- A large, phase 3 RCT (POSEIDEN) compared the combination of Imfinzi (durvalumab) + Imjudo (tremelimumab) + platinum chemotherapy with platinum chemotherapy alone in adults with metastatic, previously untreated NSCLC. [3 4]
    * The trial excluded patients with sensitizing EGFR and ALK genetic alterations and symptomatic brain metastases. Approximately 64% of the population had tumors that were PD-L1-positive (PD-L1 TC $\geq$ 1%).
    * An OS advantage in favor of Imjudo (tremelimumab) + Imfinzi (durvalumab) + platinum chemotherapy was reported in the trial (HR 0.72 [95% CI: 0.65, 0.92]; p=0.003).
- Limitations of the evidence include but are not limited to: It is not known how Imjudo (tremelimumab) + Imfinzi (durvalumab) + platinum chemotherapy compares with Keytruda (pembrolizumab) + platinum chemotherapy which is the gold standard in this treatment setting based on NCCN guidelines. [2]
- There have been no direct comparisons of Imjudo (tremelimumab) and Yervoy (ipilimumab), the other commercially available CTLA-4 inhibitor.

Extensive-Stage Small Cell Lung Cancer (ES-SCLC)

- The FDA approval in SCLC was based on a single phase 3 randomized controlled trial that compared Imfinzi (durvalumab) plus chemotherapy (etoposide plus carboplatin or cisplatin) with chemotherapy alone (placebo arm) in patients with untreated ES-SCLC. [5 6]
    * Subjects included in the study had no prior treatment for ES-SCLC. If they had prior treatment for limited-stage SCLC, they had to have been treated with curative intent and must have had a treatment-free interval of at least 6 months since their last chemotherapy, radiotherapy, or chemoradiotherapy.
    * Patients with untreated or symptomatic CNS metastasis were not included in the study.
    * Imfinzi (durvalumab) was initiated with chemotherapy (given for four cycles) and was then continued as maintenance until disease progression.

    * After a median follow-up of 25.1 months. Median OS was 12.9 months [95% CI: 11.3 to 14.7] and 10.5 months [95% CI: 9.3 to 11.2], respectively.
- There was a small, but statistically significant difference in OS that favored patients in the Imfinzi (durvalumab) group.
- National Comprehensive Cancer Center (NCCN) guidelines list Imfinzi (durvalumab) in combination with chemotherapy among its recommendations for initial therapy for extensive-stage SCLC. [2]
- Optimal sequencing of chemotherapy and immunotherapy in SCLC has not been studied. Sequential use of immunotherapies (e.g., PD-1/PD-L1 inhibitors) is not supported by current evidence.

Biliary Tract Cancer (BTC)

- FDA approval of Imfinzi (durvalumab) as a front-line therapy for locally advanced and metastatic BTC was based on a single phase 3 randomized, double-blind, placebo-controlled trial that compared the addition of Imfinzi (durvalumab) to gemcitabine plus cisplatin versus gemcitabine and cisplatin alone. [7]
    * Patients had no prior treatment in the advanced disease setting and had no prior exposure to immune-mediated therapy (e.g., PD-1/PD-L1 inhibitors).
    * Eighty-six percent of the population had metastatic adenocarcinoma of the biliary tract, which included intrahepatic cholangiocarcinoma (CCA), extrahepatic CCA, and gallbladder cancer. The remainder of the population had unresectable, locally advanced disease.
    * There was a small (~ 5 weeks), but statistically significant difference in OS advantage favoring the Imfinzi (durvalumab) treatment arm.
- National Comprehensive Cancer Center (NCCN) guidelines list Imfinzi (durvalumab) in combination with chemotherapy among recommendations for initial therapy for front-line use in unresectable or metastatic BTC. [2]

Hepatocellular carcinoma (HCC)

- A large, phase 3 RCT (HIMALAYA) compared the combination of Imjudo (tremelimumab) + Imfinzi (durvalumab) with sorafenib in adults with unresectable, previously untreated HCC not amenable to locoregional treatment. [8 9]
    * The majority of patients (53%) had extrahepatic spread of their disease and nearly all (99%) had Child-Pugh Class A disease (score of A5, 73%; and score of A6, 26%).
    * An overall survival (OS) advantage in favor of Imjudo (tremelimumab) + Imfinzi (durvalumab) was reported in the study.
    * The study also employed a parallel Imfinzi (durvalumab) monotherapy arm. The median OS in the Imfinzi (durvalumab) monotherapy arm was numerically similar to the median OS in the Imjudo (tremelimumab) + Imfinzi (durvalumab) arm. However, a statistical difference was not demonstrated for the comparison between Imfinzi (durvalumab) monotherapy and sorafenib. A likely reason a statistical difference was not demonstrated is because of the lack of statistical power allocated to this secondary analysis (a non-inferiority analysis was done).

Endpoint	T+D (n=393)	D (n=389)	S (n=389)	HR [95% CI]; p-value
OS, median	16.4 mos	- - - - - -	13.8 mos	0.78 [0.66, 0.92]; 0.004
OS, median	- - - - - -	16.5 mos	13.8 mos	0.86 [0.73, 1.03]; non-inferior

D = durvalumab; T+D = tremelimumab+ durvalumab; S = sorafenib

- Based on this evidence it is unclear whether the addition of Imjudo (tremelimumab) to Imfinzi (durvalumab) results in a clinically relevant improvement in OS over sorafenib relative to Imfinzi (durvalumab) alone. *(Note: Durvalumab monotherapy has not been FDA approved for advanced HCC but is listed in NCCN guidelines as a potential treatment option).*
- Imjudo (tremelimumab) + Imfinzi (durvalumab) is listed among preferred options in the NCCN guidelines for front-line use in unresectable HCC. It is not known how it compares with the other preferred front-line option. [2]

Endometrial Cancer

- A double-blind RCT [DUO-E] evaluated Imfinzi (durvalumab) versus placebo in combination with chemotherapy (carboplatin/paclitaxel) followed by maintenance therapy with Imfinzi (durvalumab) or placebo after completion of chemotherapy in patients with newly diagnosed stage III (unresectable) or stage IV (metastatic) endometrial carcinoma. The trial also enrolled patients with recurrent disease if there was a low potential for cure with radiation therapy or surgery. [10 11]
    * For patients with recurrent disease, prior chemotherapy in the adjuvant setting was allowed only if at least 12 months had passed from the time of completion of adjuvant chemotherapy to the time of relapse.
    * The trial included patients with all histologies of endometrial carcinomas (including carcinosarcomas) but excluded those with endometrial sarcoma.
    * Randomization was stratified by tumor mismatch repair status [deficient (dMMR) vs. proficient (pMMR) tumors].
    * The trial demonstrated a statistically significant improvement in progression-free survival (PFS) in the overall population; however, a preplanned subgroup analysis showed that this improvement was primarily due to patients with dMMR tumors. For this reason, Imfinzi (durvalumab) was FDA-approved in and is only covered in patients with dMMR tumors.
    * The study also employed an Imfinzi (durvalumab) plus Lynparza (olaparib) treatment arm; however, the relative PFS values for Imfinzi (durvalumab) vs. placebo and for Imfinzi (durvalumab) plus Lynparza (olaparib) vs. placebo were similar in patients with dMMR tumors suggesting no added benefit with the addition of Lynparza (olaparib) to the regimen in this population.
- The NCCN Uterine cancer guideline lists both carboplatin/paclitaxel/Keytruda (pembrolizumab) and carboplatin/paclitaxel/Jemperli (dostarlimab) as preferred, category 1 recommendations for stage III and stage IV endometrial carcinomas. The guideline has not been updated since the approval of Imfinzi (durvalumab) in this treatment area. [2]

Reauthorization Criteria:

- When coverage criteria are met, Imfinzi (durvalumab) is authorized for six months (24 weeks) of therapy, after which time documentation must be provided to establish that the medication is effective. Specifically, there must be documentation of clinical benefit, including disease stability or improvement and there is a lack of disease progression, based on an assessment of change in tumor burden.
    * The standard of care for evaluation of response to cancer immunotherapy, such as Imfinzi (durvalumab), is use of the iRECIST criteria for assessment of tumor burden. [12]
    * The iRECIST criteria include use of quantitative and qualitative criteria for assessment of change in tumor burden for target lesions and non-target lesions. [13]
        - Quantitative measurements for target lesions (tumor size and % change)
        - Qualitative evaluation for non-target lesions (present/disappeared/ unequivocal progression)
    * Documentation of benefit must include an assessment of the most recent imaging ("restaging scans") by the treating oncologist. Given the complexity of the evaluation, including use of the iRECIST criteria, Imfinzi (durvalumab) will not be reauthorized without an assessment of response to therapy, such a partial response (iPR), complete response (iCR), or stable disease (iSD).
    * Use of immunotherapy may result in pseudoprogression, due to immune and T-cell activation, which can appear similar to tumor flare. If there is documentation of potential disease progression ["unconfirmed progressive disease (iUPD)"], a shortened authorization (up to three months) may be approved to allow time for clarification of response to Imfinzi (durvalumab), including clinical re-evaluation of the patient and reimaging. Guidelines recommend reimaging for iUPD after 4-8 weeks.
    * If a patient has confirmed, unequivocal new lesions (progression of disease, iPD), additional Imfinzi (durvalumab) is not coverable. If a new lesion is equivocal, iUPD reassessment by the treating oncologist with repeat imaging would apply (as noted above).

Investigational Uses

- *Urothelial carcinoma (UC, bladder cancer)*
    * Imfinzi (durvalumab) initially received Accelerated approval as a subsequent therapy (after disease progression on a cisplatin-based chemotherapy regimen) for unresectable or metastatic bladder cancer based on tumor response rate in a non-comparative (single-arm), observational study.
    * A subsequent phase 3 trial (DANUBE study) intended to confirm the efficacy of Imfinzi (durvalumab) in the bladder cancer setting failed to demonstrate an OS advantage over standard chemotherapy. Based on this failed confirmatory trial the manufacturer voluntarily withdrew the bladder cancer indication. Because there is no proven net health benefit relative to the standard of care, the use of Imfinzi (durvalumab) for bladder cancer is considered investigational. [14]

- *Head and neck squamous cell cancer (HNSCC), recurrent or metastatic:* Imfinzi (durvalumab) failed to show an OS benefit relative to standard of care in a phase 3 trial (EAGLE study) as a front-line therapy for PD-L1-postive HNSCC. Because there is no proven net health benefit relative to the standard of care, the use of Imfinzi (durvalumab) for recurrent or metastatic HNSCC is considered investigational. [15]
- There are also ongoing studies designed to evaluate Imfinzi (durvalumab) in other solid tumors. [16]
- *Cervical cancer*
    * A phase 3, double-blind RCT [CALLA study] compared Imfinzi (durvalumab) with placebo in patients with untreated, locally advanced cervical cancer. Therapy was initiated with chemoradiotherapy, and then continued as maintenance after completion of the chemoradiotherapy. The primary endpoint was progression-free survival (PFS). [17]
    * There was no difference in PFS detected between the two treatment groups. There were five treatment-related deaths in the Imfinzi (durvalumab) treatment arm and one treatment-related death in the placebo arm.

Dosing and Administration [11]

- For ***NSCLC:***
    * *Locally advanced (unresectable, stage 3):* the dose of Imfinzi (durvalumab) is 10 mg/kg every 2 weeks or as 1500 mg every 4 weeks. It is given until disease progression, or for up to a maximum of 12 months, as consolidation therapy.
    * *Metastatic (in combination with Imjudo):* Up to 1500 mg every 3 weeks for up to 4 cycles, then 1500 mg every 4 weeks until disease progression. It is initiated in combination with Imjudo (tremelimumab) and platinum doublet chemotherapy, and then continued as monotherapy.
- For ***ES-SCLC*** the dose of Imfinzi (durvalumab) is 1500 mg every 3 weeks for 4-6 cycles followed by 1500 mg every 4 weeks as a single agent.
- For ***BTC*** the dose of Imfinzi (durvalumab) is 1500 mg every 3 weeks for up to 8 cycles (in combination with chemotherapy) followed by 1500 mg every 4 weeks as a single agent.
- For ***HCC*** the dose of Imfinzi (durvalumab) is 1500 mg every 4 weeks until disease progression. A single dose of Imjudo (tremelimumab) is given on Day 1 of Cycle 1.
- For **endometrial carcinoma** the dose of Imfinzi (durvalumab) is 1,120 mg (weight $\geq$30 kg) IV in combination with carboplatin/paclitaxel every three weeks for 6 cycles, followed by 1,500 mg IV every four weeks (as a single agent) until disease progression.

Appendix 1: FDA-Approved PD-1 and PD-L1 Blocking Monoclonal Antibody Therapies [a]
Programmed death receptor-1 (PD-1) inhibitors
Jemperli (dostarlimab)
Keytruda (pembrolizumab)
Libtayo (cemiplimab-rwlc)
Loqtorzi (toripalimab)
Opdivo (nivolumab)
Tevimbra (tislelizumab)
Zynyz (retifanlimab)
Programmed death-ligand 1 (PD-L1) inhibitor
Bavencio (avelumab)
Imfinzi (durvalumab)
Tecentriq (atezolizumab)

[a] Or as listed on the FDA.gov website.

Cross References
Molecular Analysis for Targeted Therapy of Non-Small Cell Lung Cancer (NSCLC), Medical Policy Manual, Genetic Testing Policy No. 56
Bavencio, avelumab, Medication Policy Manual, Policy No. dru499
Imjudo, tremelimumab, Medication Policy Manual, Policy No. dru737
Keytruda, pembrolizumab, Medication Policy Manual, Policy No. dru367
Libtayo, cemiplimab, Medication Policy Manual, Policy No. dru565
Opdivo, nivolumab, Medication Policy Manual, Policy No. dru390
Tecentriq, atezolizumab, Medication Policy Manual, Policy No. dru463

Codes	Number	Description
HCPCS	J9173	Injection, durvalumab (Imfinzi), 10 mg

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Revision History

Revision Date	Revision Summary
9/19/2024	**Effective 1/1/2025:** Changed reauthorization from 'may' to 'shall.' Operationally, all approvals will be for 24 weeks (6 months). Ongoing therapy (beyond 24 weeks) will be subject to reauthorization review every 24 weeks, for documentation of disease stability or improvement and lack of disease progression.
9/19/2024	**Effective 12/1/2024** • Added coverage criteria for locally advanced and metastatic dMMR endometrial carcinoma as a front-line therapy (no prior therapy in the advanced disease setting) when used in combination with carboplatin and paclitaxel (new indication). • Added cervical cancer and endometrial sarcoma to the list of investigational uses.
12/7/2023	No criteria changes with this annual review.
3/16/2023	• Added coverage for metastatic NSCLC as first-line therapy when used in combination with Imjudo (tremelimumab) and a platinum doublet. *[new indication].* • Added coverage for unresectable HCC as a first-line therapy when used in combination with a priming dose of Imjudo (tremelimumab). *[new indication].*
12/9/2022	Effective 1/15/2023: • Updated standard language in policy. • Added coverage for front-line use in advanced biliary tract cancer (BTC), a new indication. • Added use in second- and subsequent-line BTC as investigational.
4/21/2021	• Removed coverage criteria for urothelial carcinoma (bladder cancer) as FDA indication withdrawn due to failed confirmatory trial. Use in urothelial carcinoma (bladder cancer) moved to 'investigational' section. • Simplified coverage criteria for ES-SCLC to facilitate administration of the policy (removed criterion describing allowed prior treatments in limited-stage SCLC and removed criterion stating member should not have steroid-dependent CNS metastasis). • Standardized language relating to 'No prior PD-1/PD-L1 therapy' so it is consistent across the PD-1/PD-L1 set of policies. • Updated 'Quantity Limitations' section to reflect newly approved dosing parameters for NSCLC (added 'up to 1500 mg every 4 weeks'). • COT language updated (No change to intent of coverage criteria).
10/28/2020	Added coverage criteria for use in extensive-stage small cell lung cancer, a newly FDA approved indication.

Revision Date	Revision Summary
1/22/2020	• Added continuation of therapy (COT) criteria (no change to intent of coverage criteria). • The allowed duration of therapy for urothelial carcinoma was corrected (may be given until progression of disease).
10/23/2019	No criteria changes with this annual update.
6/15/2018	Added coverage criteria use in non-small cell lung cancer.
9/8/2017	New policy.

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Medication Policy Manual | **Policy No:** dru504

Topic: Brineura, cerliponase alfa | **Date of Origin:** July 14, 2017

Committee Approval Date: March 21, 2024 | **Next Review** 2025

Effective Date: June 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Brineura (cerliponase alfa) is used to treat pediatric patients with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2). CLN2 is an ultra-rare inherited disorder caused by an enzyme deficiency that primarily affects the nervous system.[1] Brineura (cerliponase alfa) is administered once every other week directly into the brain by intracerebroventricular infusion.

Policy/Criteria

Most contracts require pre-authorization approval of Brineura (cerliponase alfa) prior to coverage.

I. Continuation of therapy (COT): Brineura (cerliponase alfa) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note: *Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Brineura (cerliponase alfa) may be considered medically necessary in patients when there is clinical documentation (including, but not limited to chart notes) that criteria A, B, and C, below are met.

A. A diagnosis of **late infantile neuronal ceroid lipofuscinosis type 2** (CLN2) established by a pediatric neurologist, pediatric epileptologist, or geneticist.

AND

B. Patient is symptomatic (e.g., changes in gait, falls, or difficulty ambulating).

AND

C. The goal of treatment is to slow loss of ambulation.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Brineura (cerliponase alfa) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Brineura (cerliponase alfa) will be authorized in quantities of 300 mg every two weeks, up to 26 infusions per year.

C. Authorization shall be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

IV. Brineura (cerliponase alfa) is considered investigational when used for all other conditions.

Position Statement

Summary

- Brineura (cerliponase alfa) is a hydrolytic lysosomal N-terminal tripeptidyl peptidase used to slow the loss of ambulation in symptomatic pediatric patients with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2). The intent of this policy is to allow for coverage of Brineura (cerliponase alfa) in this population, as detailed in the coverage criteria.
- CLN2 is an ultra-rare inherited disorder caused by the deficiency of the lysosomal enzyme tripeptidyl peptidase.
- There are no other treatment options for CLN2. Prior to the approval of Brineura (cerliponase alfa), treatment was limited to symptomatic and supportive care. [2]
- Brineura (cerliponase alfa) has not been studied for any indications other than to slow the loss of ambulation in CLN2. Therefore, its use for any other condition is considered investigational.

Clinical Efficacy

- The efficacy of cerliponase alfa was evaluated in a prospective, non-randomized, open-label, single-arm clinical study with extension trial in symptomatic pediatric patients (N=23) aged 3 to 8 years with CLN2 disease confirmed by TPP1 deficiency. [3,4]
- The primary endpoint was a 2-point decline or an unreversed score of 0 in the Motor domain of the CLN2 rating scale (0, profoundly impaired, to 3, grossly normal) at 48 weeks. [3,4]
- In the matched patient analysis, 94% of patients treated with cerliponase alfa demonstrated fewer declines in the Motor domain of the CLN2 score compared to 76% of patients in the natural history cohort after 48 weeks of follow-up. [3,4]
- During the extension phase, after 96 weeks of treatment 94% of patients treated with cerliponase alfa did not experience a decline in the Motor domain of the CLN2 Clinical Rating Scale compared to 35% of matched patients in the natural history cohort. [3,4]

- Limitations to the trial include the use of an outcome measure with a subjective endpoint in which the clinical meaningfulness of a change in score is unknown. The observational study lacks design to demonstrate cause and effect; however, the historical control group was required to meet the same baseline inclusion criteria as the treatment group and a matched patient analysis was performed to minimize bias. Although the sample size appears small, CLN2 is an ultra-rare disease, and a large study population was identified and accurately represents the overall population. A randomized, placebo-controlled trial would be unethical, and appropriate measures were taken to increase the validity of the evidence where feasible given the complexity and severity of the disease.
- CLN2 treatment guidelines list Brineura (cerliponase alfa) as a treatment option; however, medication start and stop criteria were considered out of scope for this international guideline and therefore not included. Management of CLN2 is symptomatic and palliative. Treatment is directed at mitigating manifestations of the disease: seizures, sleep-related problems, malnutrition, gastroesophageal reflux, pneumonia, hypersalivation, hyperactivity and behavior problems, psychosis, anxiety, spasticity, Parkinsonian symptoms, and dystonia. [2,5,6]

Safety

- The most commonly reported adverse reactions (incidence of 8% or more) reported with Brineura (cerliponase alfa) include pyrexia, ECG abnormalities, decreased CSF protein, vomiting, seizures, device-related complications, hypersensitivity, increased CSF protein, hematoma, headache, irritability, pleocytosis, device-related infections, bradycardia, feeling jittery, and hypotension. A commonly reported adverse event during post approval use of Brineura (cerliponase alfa) was bacterial meningitis. [3]

Codes	Number	Description
HCPCS	J0567	Injection, cerliponase alfa (Brineura), 1 mg

References

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Revision History

Revision Date	Revision Summary
3/21/2024	No criteria changes with this annual review.
3/16/2023	No changes to policy criteria with this annual update.
3/18/2022	No changes to policy criteria with this annual update.
4/21/2021	Updated COT language. No other changes with this annual update.
4/22/2020	No criteria changes with this annual update. Added COT language
4/25/2019	No criteria changes with this annual update.
2/16/2018	No criteria changes with this annual update.
7/14/2017	New Policy.

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Medication Policy Manual

Policy No: dru510

Topic:

- Radicava, edaravone
- Radicava ORS, edaravone oral suspension

Date of Origin: August 11, 2017

Committee Approval Date: June 17, 2022

Next Review Date: December 2022

Effective Date: September 1, 2022

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Radicava and Radicava ORS (edaravone) are medications for the treatment of amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease.

Policy/Criteria

Most contracts require pre-authorization approval of Radicava and Radicava ORS (edaravone)

I. Continuation of therapy (COT): Radicava and Radicava ORS (edaravone) may be considered medically necessary for COT when full policy criteria below are met, including reauthorization criteria and quantity limit. Diagnostic criteria as well as the BASELINE functional status, including the standard functional testing, prior to initiation of edaravone (Radicava) must be provided.

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Radicava and Radicava ORS (edaravone) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A through F below are met.

A. **For provider-administered (IV) Radicava (edaravone) only:** Site of care administration requirements are met. [refer to Regence Pharmacy Services Medication Policy Manual, Site of Care Review, dru408]

AND

B. A diagnosis of **amyotrophic lateral sclerosis (ALS),** established by or in consultation with specialist in neurology or ALS.

AND

C. Disease duration of two years or less.

AND

D. Currently taking riluzole, unless riluzole has been ineffective, contraindicated, or not tolerated.

AND

E. The patient has a score of greater than or equal to two on all items of the ALS functional rating scale (ALSFRS-R) at the start of treatment.

AND

F. Normal respiratory function [defined as a forced vital capacity (FVC) ≥80%] at the start of treatment

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers intravenous Radicava (edaravone) coverable only under the medical benefit (as a provider-administered medication).

B. Regence Pharmacy Services considers Radicava ORS (edaravone oral solution coverable only under the pharmacy benefit (as a self-administered medication).

C. When pre-authorization is approved, intravenous Radicava (edaravone) will be authorized in quantities of up to 134 infusions per year, based on the prescribing information.

D. When pre-authorization is approved, Radicava ORS (edaravone oral solution) will be authorized as follows:

Initial Cycle: Up to 2 starter packs (70ml) will be authorized for the initial 28 days of treatment, based on daily dosing for 14 days, followed by a 14-day drug-free period.

Subsequent Cycles (maintenance): Up to 50ml will be authorized per 28 days, based on daily dosing for 10 days out of 14-day periods, followed by 14-day drug-free periods

E. Authorization may be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, including disease stability or improvement, as demonstrated by stabilization or improvement in baseline ALSFRS-R or other measures of function.

IV. Edaravone (Radicava) is considered investigational when used for all other conditions, including but not limited to:

A. Acute ischemic stroke

B. In patients with ALS and an FVC of less than 80% at the start of treatment**.**

Position Statement

Summary

- ALS is a neurodegenerative disease characterized by loss of motor neurons in the spinal cord, brainstem, and motor cortex. As the disease progresses individuals lose strength and the ability to move their arms, legs, and body. Progression of the disease also leads to a decline in respiratory function.
- Edaravone (Radicava) is an intravenously infused medication indicated for the treatment of amyotrophic lateral sclerosis (ALS).
- The intent of the criteria is to limit use to patients with a diagnosis of ALS, for the indications, regimen, and dose for which it has been studied, as detailed in the coverage criteria (diagnosed in the past two years and are currently taking or have failed riluzole). Patients must also have a forced vital capacity of at least 80% at baseline and a score of at least 2 on all 12 items of ALSFRS-R, a measure of functional impairment.
- Edaravone (Radicava) demonstrated efficacy in ALS patients with normal respiratory function in one randomized, placebo-controlled phase 3 study.
    * All patients had a diagnosis of definite or probably ALS and a disease duration of less than two years.
    * A score of at least 2 on all 12 items of ALSFRS-R. The ALSFRS-R is a validated measure of functional impairment. Scores of at least 2 indicate that functionality of most activities of daily living.

    * Patients were required to have a forced vital capacity (FVC) of at least 80% at baseline.
    * Most patients in the study were taking riluzole at baseline.
- While edaravone (Radicava) is approved for ALS, it has only been shown to be beneficial in a subset of patients.
- Edaravone (Radicava) did not show any benefit in an earlier phase 3 study that was conducted in a broader population that include patients with more advanced respiratory dysfunction (FCV <80% at the start of treatment). FVC may be measured in an upright or supine position.
- American Academy of Neurology (AAN) guidelines recommend that riluzole should be offered to slow disease progression. The guidelines have not been updated to include edaravone (Radicava) .
- The recommended dosing for the initial treatment cycle of edaravone (Radicava) is 60 mg IV given daily for 14 days followed by a 14-day drug free period. In subsequent treatment cycles edaravone (Radicava) is given at a dose of 60 mg IV for 10 days followed by a 14-day drug free period. The safety and effectiveness of higher doses have not been established.
- The safety and effectiveness of edaravone (Radicava) in conditions other than ALS have not been established.

Clinical Efficacy [1,2]

- One phase 3 randomized, controlled trial (RCT) was used to support FDA approval.
    * The study was conducted entirely in Japan and included newly diagnosed patients with ALS.
        - All patients had a diagnosis of definite or probably ALS and a disease duration of less than two years.
        - A score of at least 2 on all 12 items of ALSFRS-R. The ALSFRS-R is a validate measure of functional impairment, scores of at least 2 indicate that functionality is maintained for most activities of daily living.
        - Patients were required to have a forced vital capacity (FVC) of at least 80% at baseline.
        - Most patients in the study were taking riluzole at baseline.
    * The primary endpoint was change in the revised ALS functional rating scale (ALSFRS-R), a validated rating instrument for monitoring the progression of disability in patients with ALS.
    * Edaravone (Radicava) was shown to slow the reduction in ALSFRS-R compared to placebo.
- Edaravone (Radicava) did not demonstrate benefit compared to placebo in an earlier study which was conducted in a broader population. However, a post-hoc analysis identified that there may have been benefit in patients with preserved respiratory function, thus a second phase 3 study was designed to investigate efficacy in this narrow population and support regulatory approval.

Guidelines

- American Academy of Neurology (AAN) guidelines recommend that riluzole be offered to slow disease progression in patients with ALS. The AAN concluded that riluzole has a modest beneficial effect in slowing disease progression and cohort studies suggest riluzole may be associated with longer survival. [3]
- AAN guidelines have not been updated to include edaravone (Radicava).

Revised ALS Functional Rating Scale (ALSFRS-R) [4]

- The ALSFRS-R is a questionnaire-based scale that assesses the ability of patients to perform activities of daily living (ADLs). Scores range from 0 (worst) to 48 (normal)
- It consists of 12 functional domains and each item is rated from 0 to 4, with higher scores indicating better function.
- The 12 domains are speech, salivation, swallowing, handwriting, cutting food, dressing and hygiene, turning in bed, walking, climbing stairs, orthopnea, and respiratory insufficiency.

Investigational Uses

- Although edaravone (Radicava) has been studied for the treatment of acute ischemic stroke, the evidence is currently preliminary. Larger, well controlled trials are needed to establish the safety and efficacy of edaravone (Radicava) in this setting. [5,6]
- Edaravone (Radicava) has only efficacy in patients with an FVC of greater than or equal to 80% at the start of treatment. [1,2] Additional studies are needed to establish efficacy in patients with lower baseline FVC.

Codes	Number	Description
HCPCS	J1301	Injection, edaravone (Radicava), 1 mg

Cross References
Infused Medication Alternative Site of Care, Medication Policy Manual, Policy No. dru408

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Revision History

Revision Date	Revision Summary
6/17/2022	Added Radicava ORS (edaravone oral solution) to policy.
1/20/2021	No criteria changes with this annual review.
01/22/2020	- Added continuation of therapy (COT) criteria (no change to intent of coverage criteria). - Clarify reauthorization criteria (including use of ALSFRS-R scoring or other measure of function).
1/31/2019	Updated reauthorization criteria to clarify that clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement. Clarified initial documentation requirements (no change to intent).
2/19/2018	- Clarified that the patient must have a score of greater than or equal to 2 on the ALSFRS-R at the start of treatment. - Clarified that use in patients with an FVC of less than 80% at the start of treatment is considered investigational.
8/11/2017	New policy (effective 8/11/2017)

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Medication Policy Manual | **Policy No:** dru517

Topic: New to Market Drugs and Indications | **Date of Origin:** August 2017

Committee Approval Date: September 19, 2024 | **Next Review Date:** 2025

Effective Date: January 1, 2025

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

The intent of the New to Market Drugs and Indications pre-authorization criteria is to ensure appropriate use of newly approved ("new-to-market") medications, as well as newly approved indications for existing medications, as outlined in Food and Drug Administration (FDA) approved product labeling while full medication policy criteria are being developed (new or updated medication policies). Appropriate use is defined as use in patients who have an FDA approved indication, would meet the inclusion/exclusion criteria for the pivotal trials, who are receiving the FDA labeled dose, and who do not have any FDA labeled contraindications.

Policy/Criteria

Most contracts require pre-authorization approval of new to market drugs (NTMDs) and existing medications used for new indications (EMFNI) prior to coverage.

I. Continuation of therapy (COT):

NTMDs may be considered medically necessary for COT when criteria A and B below are met.

EMFNI may be considered medically necessary for COT when there is clinical documentation (including, but not limited to chart notes) confirming that criteria A, B, and C below are met.

A. The patient is established on this therapy prior to current health plan membership AND the medication was covered by another health plan.

***Note**: If the diagnosis is not an FDA approved indication, written documentation of coverage must be provided, such as an approval letter or paid claim.*

AND

B. If the diagnosis is not an FDA approved indication, documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria, is provided.

AND

C. ***EMFNI only:*** There are no specific COT criteria built into the drug-specific medication policy.

PLEASE NOTE: Specific COT criteria in drug-specific medication policies take precedence over the general criteria listed in this policy.

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): **NTMDs** and **EMFNI** may be considered medically necessary for coverage when criteria A through D below are met.

A. The patient has an FDA approved indication for the requested medication.

AND

B. The patient would meet the inclusion and exclusion criteria for the pivotal trial(s) for the requested FDA approved indication, as detailed in *Appendix A*.

AND

C. The patient does not have any FDA labeled contraindications to the requested medication.

AND

D. The quantity requested is within the manufacturer's FDA labeled maximum dose and duration.

III. Administration, Quantity Limitations, and Authorization Period

A. For the scope of this coverage policy, self-administered or provider-administered drug status will be determined by product specific labeling and prescribing information.

B. When prior authorization is approved, the requested medication may be authorized in quantities (including dose and duration) that are reasonably safe and effective based on information contained in the FDA approved labeling.

C. Authorization **shall** be reviewed at least annually (shorter, for drugs with data of uncertain safety/efficacy or in indications dictating a shorter duration of use, such as, neoadjuvant therapy), until applicable drug-specific policy has been updated and developed for **NTMDs** and **EMFNI**.

1. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

2. OF NOTE: For new medications (or indications) approved under the FDA's accelerated approval regulations, continued approval for the medication/indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. If confirmatory trials fail to show clinical benefit, the coverage may be considered not medically necessary and may not be continued, per the terms of the health plan contract.

IV. New to market drugs and existing medications used for new indications are considered investigational when used for all other conditions not listed in their FDA approved prescribing information, as described in the criteria above.

Appendix A: Sources for Determination of Inclusion and Exclusion Criteria for the Pivotal Trial
The intent is limiting coverage to requests that mirror how the drug and indication was studied in the clinical trials used for the FDA approval. The following sources will be considered for determination of inclusion and exclusion criteria for the pivotal trial: • "Section 14 Clinical Trials" of the FDA-approved product labeling • clinicaltrials.gov (based on the NCT) • The "Methods" section in the published trial (if available) • The pivotal trial protocol(s) (if available) Major considerations include the diagnostic criteria, prior therapies (line in therapy), and dosing regimen, including use of mono- or combination therapy (if applicable).

NCT = national clinical trial number

Revision History

Revision Date	Revision Summary
9/19/2024	Clarified authorization period. Removed criteria "the prescribed dose cannot be achieved using a lesser quantity of a higher strength" (criterion IID2), to be consistent with intent of policy. No changes to intent of criteria.
9/14/2023	Clarified COT criteria requirements (no change to intent of coverage criteria).
12/9/2022	Added clarity to authorization period, indicating that authorizations are 12 months unless the label indicates a shorter duration of use.
10/15/2021	Clarified authorization limit. No change to intent of policy criteria.
10/26/2020	Added continuation of therapy (COT) criteria (no change to intent of coverage criteria).
7/24/2019	• Updated criteria to add review of new indications for existing medications, in addition to newly approved medications ("new to market drugs"). • Add criteria for review of requests versus pivotal trial inclusion and exclusion criteria, to mirror the rationale for the FDA labeling.
8/17/2018	No updates to criteria on this annual review.
9/8/2017	New policy (effective 1/1/2018).

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Medication Policy Manual

Policy No: dru523

Topic: Chimeric Antigen Receptor (CAR) T-Cell Therapies:

- Abecma, idecabtagene vicleucel
- Aucatzyl, obecabtagene autoleucel
- Breyanzi, lisocabtagene maraleucel
- Carvykti, ciltacabtagene autoleucel
- Kymriah, tisagenlecleucel
- Tecartus, brexucabtagene autoleucel
- Yescarta, axicabtagene ciloleucel

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IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Chimeric antigen receptor (CAR) T-cell therapies are immunotherapies that target specific types of cancer. CAR T therapies are made for each patient, from the patient's own blood cells. CAR T therapies target and kill cancer cells.

Policy/Criteria

Most contracts require pre-authorization approval of CAR T-cell therapies prior to coverage.

I. CAR T-cell therapies are considered investigational, except for those situations specifically addressed in the policy criteria below.

PLEASE NOTE: Under this criterion, any products not specifically addressed in this policy will be considered investigational.

II. Continuation of therapy (COT): CAR T-cell therapies may be considered medically necessary when full policy criteria below are met, including quantity limit. However, CAR T-cell therapy is not coverable for repeated doses and is not coverable if a patient has previously received prior CAR T-cell therapy (including, but not limited to those listed in *Appendix 5*).

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

III. New starts (treatment-naïve patients): CAR T-cell therapies may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that the patient has one of the following CAR T-cell therapy specific coverable diagnoses listed and meets all the requirements in criterion 1, 2, 3, 4, 5, or 6 below:

1. **B-cell acute lymphoblastic leukemia** (ALL) – Aucatzyl (obecabtagene autoleucel), Kymriah (tisagenlecleucel) and Tecartus (brexucabtagene autoleucel) only:

a. Diagnostic	AND	b. Documentation of relapsed/refractory disease	AND	c. Step therapy	AND	d. Suitability for CAR T
BOTH of the following: **i.** There is morphologic marrow tumor involvement (≥ 5% lymphoblasts). **AND** **ii.** Current confirmation of CD19 tumor expression.		One of the following: **i.** ALL has **relapsed after an allogeneic stem cell transplant** (SCT) and CAR T-cell therapy is infused after SCT as follows: a) **Kymriah only:** infused 6 months or more after SCT. b) **Tecartus, and Aucatzyl only:** infused 100 days or more after SCT. **OR** **ii.** ALL is refractory, as defined by ONE of the following: a) An initial complete remission is not achieved after two cycles of chemotherapy. b) A complete remission is not achieved after one cycle of chemotherapy for ALL that relapses after an initial complete remission. **OR** **iii.** ALL has relapsed after a second- or subsequent complete remission (post-chemotherapy).		**For Philadelphia chromosome positive ALL** (Ph+ ALL) only: the patient is refractory to, or relapsed after, treatment with two or more tyrosine kinase inhibitors (TKIs) indicated for ALL, unless the patient has intolerance or contraindications to the TKIs indicated for ALL (see *Appendix 1*).		ALL of the following: **i.** Age requirements met, as defined in Table 1. **AND** **ii.** Patient is fit for therapy, as defined in *Table 2*. **AND** **iii.** No prior use of gene therapy (see *Appendix 5*).

Table 1: Age requirements for CAR T-cell therapy [a]

Diagnosis	CAR T-cell product	Age criterion
B-cell ALL	Kymriah (tisagenlecleucel)	The patient is 25 years old or younger at the time of infusion.
B-cell ALL	Aucatzyl (obecabtagene autoleucel) and Tecartus (brexucabtagene autoleucel)	The patient is 18 years old or older at the time of infusion.

[a] **PLEASE NOTE:** Age criteria are based on clinical trials and aligned with FDA approved labeling.

2. Follicular lymphoma (FL) *(not "transformed")* [b] **-** Breyanzi (lisocabtagene maraleucel), Yescarta (axicabtagene ciloleucel), and Kymriah (tisagenlecleucel) only:

a. Diagnostic:	**AND**	**b. Documentation of relapsed/refractory disease**	**AND**	**c. High risk of relapse**	**AND**	**d. Suitability for CAR T**
BOTH of the following: **i.** Patient is diagnosed with stage III or IV FL. **AND** **ii.** The FL has not "transformed" (grade IIIb) to a more aggressive lymphoma, such as DLBCL. [b]		Disease has progressed following two or more prior FL chemotherapy regimens. *Prior therapy must have included an anti-CD20 monoclonal antibody, and an alkylating agent (such as bendamustine, cyclophosphamide, or chlorambucil).*		One of the following: **i.** Disease has progressed within 24 months of initiation of the first line of anti-CD20 monoclonal antibody. **OR** **ii.** Disease has progressed within 6 months of completion of the most recent FL chemotherapy regimen.		BOTH of the following: **i.** Patient is fit for therapy, as defined in *Table 2*. **AND** **ii.** No prior use of gene therapy (see *Appendix 5*).

[b] **PLEASE NOTE**: For patients with grade IIIb (transformed FL), please use the DLBCL criteria, for consideration of coverage.

3. Mantle-cell lymphoma (MCL) - Breyanzi (lisocabtagene maraleucel) and Tecartus (brexucabtagene autoleucel) only:

a. Documentation of relapsed/refractory disease	AND	b. Suitability for CAR T
One of the following: **i.** Disease is refractory to two or more prior chemotherapy regimens. [c] **OR** **ii.** Disease has relapsed following a second or subsequent complete remission (post chemotherapy or chemoimmunotherapy). [c]		BOTH of the following: **i.** Patient is fit for therapy, as defined in *Table 2*. **AND** **ii.** No prior use of gene therapy (see *Appendix 5*).

[c] **PLEASE NOTE:** Prior therapy must have included an anti-CD20 monoclonal antibody, an anthracycline or bendamustine, and a Bruton's tyrosine kinase (BTK) inhibitor (see *Appendix 3*).

4. **Large B-cell lymphoma -** Breyanzi (lisocabtagene maraleucel), Kymriah (tisagenlecleucel), or Yescarta (axicabtagene ciloleucel) only:

a. Diagnostic	AND	b. Documentation of relapsed/refractory disease	AND	c. No active <u>primary</u> CNS disease	AND	d. Suitability for CAR T
One of the following: **i. Diffuse large B-cell lymphoma** (DLBCL), not otherwise specified (NOS). **OR** **ii.** High-grade B-cell lymphoma. **OR** **iii.** DLBCL arising from follicular lymphoma (transformed FL). **OR** **iv. <u>For Yescarta and Breyanzi only:</u>** Primary mediastinal large B-cell lymphoma (PMBCL).		One of the following: **i.** Disease is refractory to two or more prior chemotherapy regimens. [d] **OR** **ii.** Disease has relapsed following a second- or subsequent complete remission (post chemotherapy). [d] **OR** **iii.** For DLBCL arising from FL: disease is refractory to, or relapsed after, two or more prior chemotherapy regimens <u>after</u> transforming to DLBCL. [d] **OR** **iv. <u>For Yescarta and Breyanzi only:</u>** Disease is refractory to first-line chemotherapy (primary refractory). [de] **OR** **v. <u>For Yescarta and Breyanzi only:</u>** Disease relapsed within 12 months of a first-line complete remission (post chemotherapy). [d]		Patient does not have active <u>primary</u> central nervous system (CNS) disease.		BOTH of the following: **i.** Patient is fit for therapy, as defined in *Table 2*. **AND** **ii.** No prior use of gene therapy (see *Appendix 5*).

[d] **PLEASE NOTE:** Prior therapy must have included an anti-CD20 monoclonal antibody for CD20-positive tumors ("chemoimmunotherapy"), and an anthracycline-containing regimen.

[e] **PLEASE NOTE:** Primary refractory is defined as no complete remission to 1st-line therapy. Intolerance to 1st-line therapy does not meet intent of this criteria.

5. Multiple myeloma (MM) - Abecma (idecabtagene vicleucel) and Carvykti (ciltacabtagene autoleucel) only:

A. Documentation of relapsed/ refractory disease	**AND**	**B. Step therapy**			**AND**	**C. Suitability for CAR T**
One of the following: **i.** For Abecma: Disease is relapsed after, or refractory to, two or more prior MM regimens including an immunomodulatory agent, a proteosome inhibitor, and an anti-CD38 monoclonal antibody (see *Appendix 4*). **OR** **ii.** For Carvykti: Disease is relapsed after, or refractory to, one or more prior MM regimens including an immunomodulatory agent and a proteosome inhibitor AND is refractory to lenalidomide (see *Appendix 4*).		**Prior HSCT** Patient has had a prior HSCT, unless contraindicated.	**AND**	**No prior BCMA therapy** No prior use of therapy directed against B-cell maturation antigen, such as Blenrep (belantamab mafodotin), Elrexfio (elranatamab), or Tecvayli (teclistamab).		BOTH of the following: **i.** Patient is fit for therapy, as defined in *Table 2*. **AND** **ii.** No prior use of gene therapy (see *Appendix 5*).

HSCT: hematopoietic stem cell transplant [bone marrow transplant (BMT)].

6. Chronic lymphocytic leukemia (CLL) and **Small lymphocytic lymphoma** (SLL) - Breyanzi (lisocabtagene maraleucel) only:

a. Documentation of relapsed/ refractory disease	AND	b. No active CNS disease	AND	c. Suitability for CAR T
The patient has disease refractory to or relapsed after three or more prior CLL/SLL therapies including a Bruton's tyrosine kinase (BTK) inhibitor-based regimen and a Venclexta (venetoclax)-based regimen.		The patient does not have active central nervous system (CNS) disease.		BOTH of the following: **i.** Patient is fit for therapy, as defined in *Table 2*. **AND** **ii.** No prior use of gene therapy (see *Appendix 5*).

Table 2: Suitability for CAR T-cell therapy

The patient is a suitable candidate for CAR T-cell therapy and meets all the following criteria 1 through 3 below:
1. The patient has an ECOG performance status of 0 or 1 [or Karnofsky Performance score (KPS) of at least 80; the patient is ambulatory and able to carry out work of a light or sedentary nature].
AND
2. The patient has adequate and stable kidney, liver, and cardiac function (provider attestation).
AND
3. The patient has no active systemic infections (including, but not limited to HCV, HBV, and HIV infection) (provider attestation). **PLEASE NOTE:** Suitability for CAR-T therapy must be documented in recent clinical documentation (such as in chart notes, laboratory reports), which may include evaluation for a hematopoietic stem cell transplant [HSCT; bone marrow transplant (BMT)].

IV. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers chimeric antigen receptor (CAR) T-cell therapies coverable only under the medical benefit (as provider-administered medications).

B. When pre-authorization is approved, CAR T-cell therapies will be authorized in quantities of one treatment course per lifetime.

V. Investigational Uses:

A. Repeated doses of CAR T-cell therapies (see *Appendix 5*), including for CAR T previously given as part of a clinical trial.

B. CAR T-cell therapies are considered investigational for all other conditions not specifically addressed in the coverage criteria defined above.

Position Statement

Summary

- There are multiple CAR T-cell therapies undergoing study for the treatment of several different types of cancers. Most of these therapies are still in early stages of development. Further study is necessary to determine whether they are safe and effective.
- CAR T-cell therapies are adoptive immuno-therapies in which T-cells are removed from the body and genetically engineered to recognize cancer cells that express an antigen receptor protein, such as CD-19 or B-cell maturation antigen (BCMA). They are known as "CAR-T cells". The harvest and reinfusion of the T-cells is a complex procedure requiring precise scheduling and coordination of resources.
- In addition to coverage criteria set forth in this medication policy, patients must also meet stringent eligibility criteria set forth by the manufacturers of each CAR T-cell therapy.
- Patients meeting criteria for CAR T-cell therapy will be enrolled in a health plan care management program.
- The intent of this policy is to allow for coverage of these CAR T-cell therapies for the specific diagnoses for which they have been studied and to limit coverage to doses studied and shown to be safe and effective in clinical trials.
- In pivotal trials for initial FDA approval of CAR-T therapies, patients were required to have adequate performance status (PS), stable and adequate organ function, no active infections, and no graft-versus-host disease (GVHD). Recent clinical documentation must be provided, including documentation of ECOG performance status and/or Karnofsky Performance score (KPS) score. In addition, all patients were also required to be naïve to prior immunotherapy and gene therapy, including prior CAR T-cell therapy.
- Most pivotal trials required failure of standard therapy, such as (but not limited to):
  * an anti-CD20 monoclonal antibody [e.g., rituximab].
  * standard chemotherapy, such as an anthracycline-containing (e.g., doxorubicin) chemotherapy regimen for large B-cell lymphoma or an alkylator for follicular lymphoma (FL).
  * Use of targeted tyrosine kinase inhibitors [Ph+ acute lymphoblastic leukemia

(ALL) and mantle cell lymphoma (MCL)].
    * use of standard multiple myeloma (MM) therapies (a proteosome inhibitor, an immunomodulatory agent, and an anti-CD38 antibody).
- There is interest in using CAR T-cell therapies in earlier stages of disease than they were initially studied and approved, as well as use of CAR T after other targeted therapies. Although there are several ongoing studies that indicate they may have activity in these settings, there has also been a more critical look at the potential safety of these products, particularly surrounding their potential for causing secondary malignancies. Until a more accurate benefit versus risk is sorted out, CAR T therapies are only coverable after the number of prior lines of therapy and regimens specified in the coverage criteria.
- Administration of CAR T-cell therapy can result in cytokine release syndrome (CRS) which may cause fatal or life-threatening reactions. More recently the FDA has proposed that CAR-T products include a boxed warning for T-cell malignancies.
- CAR T-cell therapy is given via an intravenous infusion as a one-time infusion. Repeat doses have not been adequately studied.
- Although there is interest in the use of CAR T-cell therapies in other diagnoses, including in patients with primary CNS lymphoma, the use of CAR T-cell therapies in other diagnoses, except as specified in the coverage criteria above, are considered unproven ("investigational"), along with use of repeated doses of CAR T-cell therapies. Many trials are ongoing in various diagnoses as well as for various dosing regimens.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy

KYMRIAH (TISAGENLECLEUCEL)

- Kymriah (tisagenlecleucel) has been studied in, and is FDA-approved for:
  - * B-cell precursor ALL that expresses the CD19 antigen and is refractory to, or in a second or later relapse after, treatment with standard chemotherapy, in patients up to 25 years of age.
  - * Large B-cell lymphoma that is relapsed after or refractory to two or more prior lines of systemic therapy. This indication specifically includes diffuse large B-cell lymphoma (DLBCL), not otherwise specified; high-grade B-cell lymphoma; and DLBCL arising from follicular lymphoma (FL). The indication does not include use in primary central nervous system (CNS) lymphoma.
  - * Follicular lymphoma (FL) that has relapsed after two or more prior lines of systemic therapy for FL.

B-cell precursor acute lymphoblastic leukemia (ALL):

- In single-arm, clinical studies Kymriah (tisagenlecleucel) demonstrated high rates of complete remission in children and young adults with refractory or relapsed, CD19-positive, precursor B-cell ALL. All patients who achieved complete remission were also minimal residual disease negative which is predictive of survival. A small, single-arm clinical trial (ELIANA; N = 63 at the interim analysis for the FDA approval [1] and n=75 in the published trial [2]) evaluated remission rates in pediatric and young adult patients 25 years and younger with refractory or recurrent CD19-positive, B-cell precursor ALL.
  - * Subjects had a median of three prior therapies. Fifty six percent received a prior hematopoietic stem cell transplant (HSCT).
  - * The primary endpoint was complete remission (CR), or CR with incomplete blood recovery (CRi), sustained for 4 weeks within three months after infusion (refer to Appendix 2 for remission definitions).
  - * An ORR was achieved in 82.5% of the subjects in the trial three months after treatment, of which 63.5% had a CR.
  - * All subjects who achieved CR were also negative for minimum residual disease (MRD) based on bone marrow findings.
- A second, smaller (N = 29), identically designed trial (ENSIGN) reported similar results. [1]
  - * CR was achieved by 69% of subjects three months after treatment.
  - * All subjects with CR were also MRD-negative.
- MRD refers to the ongoing detection of disease despite a designation of CR based on conventional pathologic analysis. In a large meta-analysis of patients with ALL, achieving MRD negativity was determined to be a substantial finding as it was consistently associated with improved survival. [3] However, use of MRD as an intermediate endpoint does not preclude the need for confirmatory trials using traditional clinically relevant endpoints.
- The safety and effectiveness of Kymriah (tisagenlecleucel) has not been established in patients over 25 years of age. In patients over the age of 25, B-cell precursor ALL is generally considered to be a different disease with a different disease course (poorer prognosis with poorer survival) such that the efficacy of Kymriah (tisagenlecleucel) cannot be presumed based on the available evidence from patients who are less than 25 years old.

- The NCCN ALL guideline lists Kymriah (tisagenlecleucel) among several recommended options for relapsed or refractory ALL. It is recommended in the following settings: [4]
    * *Philadelphia chromosome-positive ALL:* For patients 25 years and younger with refractory disease or two or more relapses, and failure of two tyrosine kinases inhibitors (TKIs).
    * *Philadelphia chromosome-negative ALL:* For patients 25 years and younger with refractory disease or two or more relapses.

Diffuse large B-cell lymphoma (DLBCL):

- Approval in large B-cell lymphoma was based on two small, single-arm, observational studies. Specifically, Kymriah (tisagenlecleucel) was studied in two, small, single-arm observational studies (low-quality evidence) that evaluated remission rates at six months in adults with relapsed or refractory DLBCL, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma (FL, also known as transformed FL). [1,5]
    * Subjects enrolled in the trials had a median of three prior therapies. Between 56% and 86% had refractory disease, and approximately half had a prior stem cell transplant (SCT).
    * Patients included in the study were required to have failed standard therapy which included an anti-CD20 monoclonal antibody [e.g., rituximab] if the tumor was CD20-positive, and an anthracycline-containing (e.g., doxorubicin) chemotherapy regimen.
    * Prior CAR T-cell therapy was not allowed.
    * Patients were required to have adequate performance status, stable and adequate organ function, no active infections, and no advanced graft-versus-host disease.
    * One of the studies required confirmation of CD19 antigen (the target of this therapy) on cancer cells, the other did not; however, the CD19 antigen is present in nearly all large B-cell lymphomas.
    * Complete remission at 6 months was observed in 32% to 57% of subjects. In one study, the median duration of remission (DoR) for those who had achieved a complete remission was 29 months (range: 7.7 to 38 months). In the other study, the median DoR has not been reached.
- Although a relatively high rate of complete remission at 6 months was observed in some patients, long-term survival and durability of effect are still being evaluated. The effects on clinically relevant outcomes are not yet known.
- A phase 3, international, randomized controlled trial (BELINDA) evaluated Kymriah (tisagenlecleucel) in patients with aggressive B-cell lymphoma that was refractory or relapsed within 12 months after receiving first-line therapy with an anti-CD20 antibody and an anthracycline-containing chemotherapy regimen. The study failed to show a difference in event-free survival (EFS), the primary endpoint, between Kymriah (tisagenlecleucel) and investigator's choice of standard of care chemotherapy. [30]
- Kymriah (tisagenlecleucel) has not been adequately evaluated in subjects with a history of central nervous system (CNS) lymphoma. In particular, there is insufficient evidence to establish the safety and efficacy of CAR T therapies in patients with primary CNS lymphoma (see *Investigational Uses* below, for additional discussion).

- The NCCN B-cell lymphoma guideline lists Kymriah (tisagenlecleucel) as a treatment option for DLBCL that is refractory to, or relapses after, at least two prior chemoimmunotherapy regimens. The guideline further states that it is not appropriate for patients who have achieved a complete response to chemoimmunotherapy. [4]

Follicular lymphoma (FL):

- In a single-arm, clinical study Kymriah (tisagenlecleucel) demonstrated high rates of complete remission (CR) in patients with relapsed or refractory FL after at least two prior systemic therapies for FL. [26]
    * Patients enrolled in the trial had grade 1, 2, and 3A FL (patients with grade 3B FL were excluded from the trial).
    * Patients with transformed FL, prior allogeneic hematopoietic SCT, and prior CAR T-cell therapy were excluded from participating in the trial.
    * Remission rate was the primary endpoint of the study. Complete remission was observed in 68% [95% CI: 57, 77] of subjects. Patients were followed for a median duration of 9.1 months. The median duration of response is not yet known.
- Although a relatively high rate of complete remission at 6 months was observed in some patients, long-term survival and durability of effect are still being evaluated. The effects on clinically relevant outcomes are not yet known.
- The NCCN B-cell lymphoma guideline lists Kymriah (tisagenlecleucel) as a treatment option for FL that is refractory to, or relapses after, at least two prior chemoimmunotherapy regimens. [4]

YESCARTA (AXICABTAGENE CILOLEUCEL)

B-cell lymphomas, including large B-cell lymphoma (DLBCL, PMBCL, transformed FL) and follicular lymphoma (FL):

Yescarta (axicabtagene ciloleucel) demonstrated high rates of response to therapy, including complete responses, in adults with relapsed or refractory B-cell lymphomas. Although results are promising, its effect on any clinically relevant outcome is not yet known.

- The pivotal single-arm trial (ZUMA-1) evaluated 101 adult large B-cell lymphoma patients who had relapsed, or were refractory to, two or more prior lines of systemic therapy. [6,7]
    * The following large B-cell lymphomas were included in the trial: Diffuse large B-cell lymphoma (DLBCL) [76%], DLBCL arising from follicular lymphoma (also known as transformed FL) [16%], and primary mediastinal B-cell lymphoma (PMBCL) [8%]. However, it does not include use in primary central nervous system (CNS) lymphoma.
    * Subjects enrolled in the trial had disease that was either refractory to the most recent therapy [77%] or relapsed within one year of autologous hematopoietic stem cell transplant (HSCT) [21%]. Enrolled patients had a median of three prior therapies for their large B-cell lymphoma.
    * For enrollment in the clinical trial, patients were required to have prior therapy that included an anti-CD20 monoclonal antibody [e.g., rituximab] if the tumor was CD20-positive, and an anthracycline-containing (e.g., doxorubicin) chemotherapy regimen.

    * Prior treatment with a CAR-T-cell therapy was not allowed.
    * Patients were required to have adequate performance status, stable and adequate organ function, no active infections, and no advanced graft-versus-host disease. They were also required to be naïve to prior immunotherapy and gene therapy, including prior treatment with Yescarta (axicabtagene ciloleucel).
    * Although Yescarta (axicabtagene ciloleucel) is designed to target the CD19 antigen on cancer cells, confirmation that the tumor cells were positive for this antigen was not required as a condition for inclusion in the study as it is present in nearly all large B-cell lymphomas.
    * The primary endpoint was overall response rate (ORR), which is based on disease involvement in the lymph nodes, organs, and bone marrow and is assessed via positron emission tomography (PET) scan or computerized tomography (CT) scan.
    * An ORR of 72% [95% CI: 62, 81] was achieved in this uncontrolled study. Of the responses, 51% [95% CI: 41, 62] were complete (CR) and 21% [95% CI: 13, 30] were partial (PR).
    * The median duration of response was 9.2 months, and was longer in those who had achieved a CR.
- An ongoing, pivotal, single-arm trial (ZUMA-5) evaluated 124 adult patients with follicular lymphoma (FL) (grade 1, 2, 3a) with measurable disease who had relapsed, or were refractory to two or more prior lines of systemic therapy, including at least one prior line of therapy that included a CD20-directed monoclonal antibody (mAb) combined with an alkylating agent. [8]
    * The majority of FL subjects enrolled in the trial had disease that was at high risk of relapsing. This included patients that were refractory to the most recent therapy [68%], which was defined as progression within 6 months of completion of the most recent prior treatment, or they were considered to be an early relapser [55%], defined as progression within 24 months of initiation of the first line of anti-CD20 containing immunochemotherapy. Due to the indolent nature of FL, it is in this population, that the benefit may outweigh the risks.
    * Enrolled patients had a median of three prior therapies for their follicular lymphoma.
    * Prior treatment with a CAR-T-cell therapy was not allowed.
    * Patients were required to have adequate performance status, stable and adequate organ function, no active infections, and no advanced graft-versus-host disease. They were also required to be naïve to prior immunotherapy and gene therapy, including prior treatment with Yescarta (axicabtagene ciloleucel).
    * Although Yescarta (axicabtagene ciloleucel) is designed to target the CD19 antigen on cancer cells, confirmation that the tumor cells were positive for this antigen was not required as a condition for inclusion in the study as it is present in the majority of FL cases.
    * The primary endpoint was overall response rate (ORR), which is based on disease involvement in the lymph nodes, organs, and bone marrow and is assessed via positron emission tomography (PET) scan or computerized tomography (CT) scan.

    * In a subset of the FL population that was evaluable (n=84), an ORR of 94% [95% CI: 62, 81] was achieved in this uncontrolled study. Of the responses, 80% were complete (CR).
    * The median duration of response and progression free survival data is immature at this time.
- The ongoing phase 3, multicenter, open-label, randomized ZUMA-7 trial studied Yescarta (axicabtagene ciloleucel) in the second-line DLBCL setting compared to standard of care (SOC) chemotherapy with intent to stem cell transplant (SCT) (n=359). [25]
    * Subjects enrolled in the trial had disease that was considered primary refractory to first line therapy [74%] or had relapsed within one year of a first-line therapy complete response [26%].
    * For enrollment in the clinical trial, patients were required to have prior chemotherapy that included an anti-CD20 monoclonal antibody [e.g., rituximab] and an anthracycline-containing (e.g., doxorubicin) chemotherapy regimen.
    * Prior treatment with a CAR-T-cell therapy was not allowed.
    * Patients were required to have adequate performance status, stable and adequate organ function, no active infections, and no advanced graft-versus-host disease. They were also required to be naïve to prior gene therapy, including prior treatment with Yescarta (axicabtagene ciloleucel).
    * Although Yescarta (axicabtagene ciloleucel) is designed to target the CD19 antigen on cancer cells, confirmation that the tumor cells were positive for this antigen was not required as a condition for inclusion in the study as it is present in nearly all large B-cell lymphomas.
    * The primary endpoint was event free survival (EFS), while PFS, tumor response (ORR), and OS were key secondary endpoints.
    * Yescarta (axicabtagene ciloleucel) improved the primary endpoint of EFS (8.3 vs. 2.0 months), as well as PFS (14.7 vs 3.7 months) and ORR (83% vs. 50%), compared to SOC chemoimmunotherapy followed by SCT. However, EFS, PFS, and ORR are unvalidated surrogate endpoints. Of note, the complete response (CR) was 62% with Yescarta (axicabtagene ciloleucel) versus 35% with SOC chemotherapy.
    * At this time, the OS data is immature. However, at a median follow-up of 47.2 months, the estimated OS at 4 years was 54.6% and 46.0% in the Yescarta (axicabtagene ciloleucel) and SOC treated groups, respectively.
- Yescarta (axicabtagene ciloleucel) has not been adequately evaluated in subjects with a history of central nervous system (CNS) lymphoma. In particular, there is insufficient evidence to establish the safety and efficacy of CAR T therapies in patients with primary CNS lymphoma (see *Investigational Uses* below for additional information).
- In addition, Yescarta (axicabtagene ciloleucel) has not been adequately evaluated in subjects who had received a prior allogeneic SCT. [6-8]
- The NCCN B-cell lymphoma guideline lists Yescarta (axicabtagene ciloleucel) as a treatment option for large B-cell lymphoma in patients with primary refractory disease, disease that has relapsed <12 months after a first-line therapy complete response, or

those that have disease that is refractory to, or relapses after, at least two prior chemoimmunotherapy regimens. In addition, Yescarta (axicabtagene ciloleucel) is listed as a treatment option for FL that is refractory to, or relapses after, at least two prior chemoimmunotherapy regimens. [4]

BREYANZI (LISOCABTAGENE MARALEUCEL)

Large B-cell lymphoma:

In a single-arm observational trial, Breyanzi (lisocabtagene maraleucel) demonstrated high rates of response, including complete responses, in adults with refractory large B-cell lymphomas. Although results are promising, its effect on any clinically relevant outcome is not yet known.

- The pivotal single-arm observational trial (TRANSCEND NHL 001) evaluated 256 adult patients who had lymphoma that had relapsed, or was refractory to, two or more prior lines of systemic therapy. [9]
    - The following types were included in the trial: Diffuse large B-cell lymphoma (DLBCL) [51%], DLBCL arising from follicular lymphoma (FL, also known as transformed FL) [22%], high-grade B-cell lymphoma (HGBCL) [13%], primary mediastinal B-cell lymphoma (PMBCL) [6%], and other B-cell lymphomas [8%]. However, it did not include use in primary central nervous system (CNS) lymphoma.
    - Subjects enrolled in the trial had disease that was either refractory to the most recent chemotherapy [67%] or relapsed within one year of autologous hematopoietic stem cell transplant (HSCT) [35%]. Enrolled patients had a median of three prior therapies for their large B-cell lymphoma.
    - Patients were required to have prior therapy that included an anti-CD20 monoclonal antibody [e.g., rituximab] if the tumor was CD20-positive, and an anthracycline-containing (e.g., doxorubicin) chemotherapy regimen. Prior treatment with a CAR-T-cell therapy was not allowed.
    - Patients were required to have adequate performance status, stable and adequate organ function, no active infections, and no advanced graft-versus-host disease.
    - Although Breyanzi (lisocabtagene maraleucel) is designed to target the CD19 antigen on cancer cells, confirmation that the tumor cells were positive for this antigen was not required as a condition for inclusion in the study as it is present in nearly all large B-cell lymphomas.
    - The primary endpoint was overall response rate (ORR), which is based on disease involvement in the lymph nodes, organs, and bone marrow and is assessed via positron emission tomography (PET) scan or computerized tomography (CT) scan.
    - An ORR of 73% [95% CI: 67, 78] was achieved in this uncontrolled study. Of the responses, 53% [95% CI: 47, 59] were complete (CR) and 20% were partial (PR).
    - At 12 months, the response rate had decreased to 54.7% [46.7, 62.0].
- The ongoing phase 3, multicenter, open-label, randomized TRANSFORM trial studied Breyanzi (lisocabtagene maraleucel) in the second-line DLBCL setting compared to standard of care (SOC) chemotherapy with intent to stem cell transplant (SCT) (n=184).[27]

    * Subjects enrolled in the trial had disease that was considered primary refractory to first line therapy [73%] or had relapsed within one year of a first-line therapy complete response [27%].
    * For enrollment in the clinical trial, patients were required to have prior chemotherapy that included an anti-CD20 monoclonal antibody (e.g., rituximab) and an anthracycline-containing (e.g., doxorubicin) chemotherapy regimen.
    * Prior treatment with a CAR-T-cell therapy or gene therapy was not allowed.
    * Patients were required to have adequate performance status, stable and adequate organ function, no active infections, and no advanced graft-versus-host disease.
    * Although Breyanzi (lisocabtagene maraleucel) is designed to target the CD19 antigen on cancer cells, confirmation that the tumor cells were positive for this antigen was not required as a condition for inclusion in the study as it is present in nearly all large B-cell lymphomas.
    * The primary endpoint was event free survival (EFS), while PFS, tumor response (ORR), and OS were key secondary endpoints.
    * Breyanzi (lisocabtagene maraleucel) improved the primary endpoint of EFS (10.1 vs. 2.3 months), as well as PFS (14.8 vs 5.7 months) and ORR (86% vs. 48%), compared to SOC chemoimmunotherapy followed by SCT. However, EFS, PFS, and ORR are unvalidated surrogate endpoints. Of note, the complete response (CR) was 66% with Breyanzi (lisocabtagene maraleucel) versus 39% with SOC chemotherapy.
    * At this time, the OS data is immature, with a median follow-up of 6.2 months.
- The ongoing phase 2, multicenter, open-label, single-arm PILOT trial studied Breyanzi (lisocabtagene maraleucel) in the second-line DLBCL setting in those deemed by the investigator, to be SCT-ineligible (n=61).[28]
    * Subjects enrolled in the trial had disease that was considered primary refractory to first line therapy [52%], had relapsed within one year of a first-line therapy complete response [23%], or had relapsed greater than one year of a first-line therapy complete response [25%].
    * For enrollment in the clinical trial, patients were required to have prior chemotherapy that included an anti-CD20 monoclonal antibody [e.g., rituximab] and an anthracycline-containing (e.g., doxorubicin) chemotherapy regimen.
    * Prior treatment with a CAR-T-cell therapy was not allowed.
    * Patients were required to be deemed ineligible for both high-dose chemotherapy and hematopoietic SCT while also having adequate organ function for CAR T-cell treatment. Of note, the demographic and baseline disease characteristics of the PILOT trial are not representative of the general transplant-ineligible population with DLBCL after one prior line of therapy. The majority of patients met the ineligibility criteria solely based on age (≥ 70 years), which is not necessarily a standard of care exclusion for SCT in practice.

    * Although Breyanzi (lisocabtagene maraleucel) is designed to target the CD19 antigen on cancer cells, confirmation that the tumor cells were positive for this antigen was not required as a condition for inclusion in the study as it is present in nearly all large B-cell lymphomas.
    * The primary endpoint was tumor response (ORR), while event free survival (EFS), PFS, and OS were key secondary endpoints.
    * For those patients that received Breyanzi (lisocabtagene maraleucel) during the PILOT trial, an ORR of 81% was achieved in this uncontrolled study. Of the responses, 54% were complete (CR) and 26% were partial (PR). At this time, the OS data is immature.
    * At the data-cut, a total of 7 patients had completed the study, 26 had ongoing follow-up, and 28 had discontinued.
    * In the transplant-ineligible population, the clinical benefit of Breyanzi (lisocabtagene maraleucel), compared to alternate therapies is unknown at this time. Given the current trial limitations in the HSCT-ineligible population, additional data is needed to assess if the benefit outweighs the known safety concerns in this population.
- Breyanzi (lisocabtagene maraleucel) has not been adequately evaluated in subjects with a history of central nervous system (CNS) lymphoma. In particular, there is insufficient evidence to establish the safety and efficacy of CAR T therapies in patients with primary CNS lymphoma (see *Investigational Uses* below, for additional discussion).
- In addition, Breyanzi (lisocabtagene maraleucel) has not been adequately evaluated in subjects who had received a prior allogeneic SCT.
- The NCCN B-cell lymphoma guideline lists Breyanzi (lisocabtagene maraleucel) as a treatment option for large B-cell lymphoma in patients with primary refractory disease, disease that has relapsed <12 months after a first-line therapy complete response, or those that have disease that is refractory to, or relapses after, at least two prior chemoimmunotherapy regimens. Of note, the guidelines list Breyanzi (lisocabtagene maraleucel) as a category 2B recommendation in the transplant ineligible population. [4]

Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL):

In a small, single-arm study Breyanzi (lisocabtagene maraleucel) demonstrated moderated rates of response to therapy, including complete remissions, in adults with relapsed or refractory CLL or SLL who had progressed after standard front-line therapies. Although results are promising, its effect on any clinically relevant outcome is not yet known.

- The pivotal single-arm trial [TRANSCEND CLL 004] evaluated 65 adult patients with relapsed or refractory CLL/SLL after prior front-line therapies. [36]
    * Subjects enrolled in the trial had disease that was either refractory or had relapsed after the most recent systemic therapy regimen which must have included both a Bruton's Tyrosine Kinase (BTK) inhibitor and a B-cell Lymphoma 2 (BCL-2) inhibitor [e.g., Venclexta (venetoclax)]. Subjects enrolled in the study had a median of five prior lines of therapy.
    * Prior treatment with a CAR-T-cell therapy or gene therapy was not allowed. Patients with Richter transformation were also excluded from the study.

    - Although Breyanzi (lisocabtagene maraleucel) is designed to target the CD19 antigen on cancer cells, confirmation that the tumor cells were positive for this antigen was not required as a condition for inclusion in the study as it is present in the majority of CLL/SLL cases.
    - The primary endpoint was objective response rate (ORR), which was defined as the incidence of a complete or partial remission using the 2018 International Workshop on Chronic Lymphocytic Leukemia (iWCLL 2018) criteria. It is based on disease involvement in the lymph nodes, organs, and bone marrow and is assessed via positron emission tomography (PET) scan or computerized tomography (CT) scan.
    - In the intent-to-treat population (ITT), an ORR of 45% was achieved in this uncontrolled study. Of the responses, 20% were complete remissions (CR) and 25% were partial remissions (PR).
    - The median duration of response (DOR) was 35 months. The DOR was greater in patients who had achieved a complete remission than in those only achieving a partial remission.
- Breyanzi (lisocabtagene maraleucel) has not been adequately evaluated in subjects with a history of central nervous system (CNS) leukemia (see *Investigational Uses* below, for additional discussion).
- In addition, Breyanzi (lisocabtagene maraleucel) has not been adequately evaluated in subjects who had received a prior allogeneic SCT.
- NCCN B-cell CLL/SLL guidelines list Breyanzi (lisocabtagene maraleucel) as a third-line treatment option for relapsed/refractory CLL/SLL, only after BTK- and Venclexta (venetoclax)-based regimens. [4]

Follicular Lymphoma (FL):

- An ongoing, pivotal, single-arm trial (TRANSCEND-FL, NCT04245839) evaluated 114 adult patients with follicular lymphoma (FL) (grade 1, 2, 3a) with measurable disease who had relapsed, or were refractory to two or more prior lines of systemic therapy, including at least one prior line of therapy that included a CD20-directed monoclonal antibody (mAb) combined with an alkylating agent. [37] A total of 139 patients were enrolled. However, 25 patients were “second line” and not included in the primary efficacy data set (n=114). [24,37]
    - The majority of FL subjects enrolled in the trial had disease that was at high risk of relapsing. This included patients that were refractory to the most recent therapy [64%], which was defined as progression within 6 months of completion of the most recent prior treatment, or they were considered to be an early relapser [50%], defined as progression within 24 months of initiation of the first line of anti-CD20 containing immunochemotherapy. Due to the indolent nature of FL, it is in this population, that the benefit may outweigh the risks.
    - Enrolled patients had a median of three prior therapies for their follicular lymphoma.
    - Prior treatment with a CAR-T-cell therapy was not allowed.

    - Patients were required to have adequate performance status, stable and adequate organ function, no active infections, and no advanced graft-versus-host disease. They were also required to be naïve to prior immunotherapy and gene therapy, including prior treatment with Breyanzi (lisocabtagene maraleucel).
    - The primary endpoint was overall response rate (ORR), which is based on disease involvement in the lymph nodes, organs, and bone marrow and is assessed via positron emission tomography (PET) scan or computerized tomography (CT) scan.
    - In a subset of the FL population that was evaluable (n=94), an ORR of 96% [95% CI: 89.5, 98.8] was achieved in this uncontrolled study. Of the responses, 73% were complete (CR). [24]
    - The median duration of response and progression free survival data is immature at this time.
- The NCCN B-cell lymphoma guideline lists Breyanzi (lisocabtagene maraleucel) as a treatment option for FL that is refractory to, or relapses after, at least two prior chemoimmunotherapy regimens. [4]

Mantle Cell Lymphoma (MCL):

In the single-arm clinical study Breyanzi (lisocabtagene maraleucel) demonstrated high rates of response to therapy, including complete responses, in adults with relapsed or refractory MCL. Although results are promising, its effect on any clinically relevant outcome is not yet known.

- The pivotal single-arm trial, MCL cohort (TRANSCEND NHL 001, NCT02631044) evaluated 88 adult patients who had relapsed or refractory mantle-cell lymphoma (MCL), after multiple specific prior therapies. [24,38]
    - Subjects enrolled in the trial had disease that was either refractory or had relapsed after the most recent chemotherapy regimen and needed to have been on an anti-CD20 monoclonal antibody [e.g., rituximab], an alkylating agent [such as an cyclophosphamide-, ifosfamide-, or bendamustine-containing chemotherapy regimen], and a Bruton's tyrosine kinase (BTK) inhibitor. Enrolled patients had a median of three prior therapies for their MCL (range 1 to 11).
    - Prior treatment with a CAR-T-cell therapy was not allowed.
    - Of note: 10% of enrolled subjects had secondary CNS lymphoma at time of enrollment in the trial. However, patients with primary CNS lymphoma were excluded.
    - The primary endpoint was objective response rate (ORR), which is defined as the incidence of a complete response or a partial response by the revised IWG Response Criteria for Malignant Lymphoma. It is based on disease involvement in the lymph nodes, organs, and bone marrow and is assessed via positron emission tomography (PET) scan or computerized tomography (CT) scan.
    - In the intent-to-treat population (ITT, n=71), an ORR of 85.3% was achieved in this uncontrolled study. Of the responses, 67.6% were complete (CR) and 17.6% were partial (PR). [24]
- NCCN B-cell lymphoma guidelines list Breyanzi (lisocabtagene maraleucel) as a third-line treatment option for relapsed/refractory MCL, only after chemotherapy and a BTK inhibitor. [4]

TECARTUS (BREXUCABTAGENE AUTOLEUCEL)

Mantle Cell Lymphoma (MCL):

In the single-arm clinical study Tecartus (brexucabtagene autoleucel) demonstrated high rates of response to therapy, including complete responses, in adults with relapsed or refractory MCL. Although results are promising, its effect on any clinically relevant outcome is not yet known.

- The pivotal single-arm trial (ZUMA-2) evaluated 74 adult patients who had relapsed or refractory mantle-cell lymphoma (MCL), after multiple specific prior therapies. [12]
    - Subjects enrolled in the trial had disease that was either refractory or had relapsed after the most recent chemotherapy regimen and needed to have been on an anti-CD20 monoclonal antibody [e.g., rituximab], an anthracycline-containing (e.g., doxorubicin) or bendamustine-containing chemotherapy regimen, and a Bruton's tyrosine kinase (BTK) inhibitor. Enrolled patients had a median of three prior therapies for their MCL.
    - Prior treatment with a CAR-T-cell therapy was not allowed.
    - Although Tecartus (brexucabtagene autoleucel) is designed to target the CD19 antigen on cancer cells, confirmation that the tumor cells were positive for this antigen was not required as a condition for inclusion in the study as it is present in the majority of MCL cases.
    - The primary endpoint was objective response rate (ORR), which is defined as the incidence of a complete response or a partial response by the revised IWG Response Criteria for Malignant Lymphoma. It is based on disease involvement in the lymph nodes, organs, and bone marrow and is assessed via positron emission tomography (PET) scan or computerized tomography (CT) scan.
    - In the intent-to-treat population (ITT), an ORR of 85% was achieved in this uncontrolled study. Of the responses, 59% were complete (CR) and 26% were partial (PR).
    - At 12 months, the estimated progression-free survival and overall survival were 61% and 83%, respectively.
- Tecartus (brexucabtagene autoleucel) has not been adequately evaluated in subjects with a history of central nervous system (CNS) lymphoma. In particular, there is insufficient evidence to establish the safety and efficacy of CAR T therapies in patients with primary CNS lymphoma (see *Investigational Uses* below, for additional discussion).
- In addition, Tecartus (brexucabtagene autoleucel) has not been adequately evaluated in subjects who had received a prior allogeneic SCT.
- NCCN B-cell lymphoma guidelines list Tecartus (brexucabtagene autoleucel) as a third-line treatment option for relapsed/refractory MCL, only after chemotherapy and a BTK inhibitor. [4]

B-cell precursor acute lymphoblastic leukemia (ALL):

- In the pivotal, single-arm, phase 2 ZUMA-3 trial, Tecartus (brexucabtagene autoleucel) demonstrated a high rate of complete remission in adults with refractory or relapsed, CD19-positive, precursor B-cell ALL. [13]

    * Subjects had a median of two prior therapies and 42% had received a prior allogeneic stem cell transplant (ASCT). In those with a prior ASCT, more than 100 days were required to pass prior to CAR-T cell therapy administration.
    * The primary endpoint was complete remission (CR) or CR with incomplete blood recovery (CRi), which was achieved in 71% of treated patients.
    * A CR was achieved in 56% of subjects treated with brexucabtagene autoleucel, while a CRi was achieved in 15%.
    * Minimum residual disease (MRD) negativity rate, based on bone marrow findings, was achieved by 97% of patients that achieved a CR/CRi.
    * The median relapse-free survival (RFS) and duration of remission were 11.6 months and 12.8 months, respectively.

- MRD refers to the ongoing detection of disease despite a designation of CR based on conventional pathologic analysis. In a large meta-analysis of patients with ALL, achieving MRD negativity was determined to be a substantial finding as it was consistently associated with improved survival. [3] However, use of MRD as an intermediate endpoint does not preclude the need for confirmatory trials using traditional clinically relevant endpoints.
- The safety and effectiveness of Tecartus (brexucabtagene autoleucel) has not been established in patients younger than 18 years of age. [14] In younger patients, B-cell precursor ALL is generally considered to be a different disease with a different disease course, such that the efficacy and safety of Tecartus (brexucabtagene autoleucel) cannot be presumed based on the available evidence from patients who are older than 18 years of age. [4]
- NCCN ALL guideline lists Tecartus (brexucabtagene autoleucel) among several recommended options for relapsed or refractory ALL and after prior tyrosine kinases inhibitors (TKIs) if Philadelphia chromosome-positive (Ph+) ALL. [4]

ABECMA (IDECABTAGENE VICLEUCEL)

Multiple Myeloma (MM):

- In the pivotal trial, Abecma (idecabtagene vicleucel) demonstrated high rates of response to therapy, including complete responses, in adults with relapsed or refractory multiple myeloma (MM). Although results are promising, the effect on any clinically relevant outcome is not yet known. The pivotal open-label, dose-finding trial (KarMMa) enrolled 140 adult patients, who had relapsed or refractory MM, after multiple specific prior therapies. However, only 128 patients received an infusion of idecabtagene vicleucel, of which, 124 received the FDA-approved dose of idecabtagene vicleucel (300-450x10^6 CAR-positive T cells). [15, 16]
    * Subjects enrolled in the trial must have received at least 3 prior MM treatment regimens, had disease that was refractory to the most recent chemotherapy regimen, and needed to have been on an anti-CD38 monoclonal antibody (mAb), a proteosome inhibitor (PI), and an immunomodulator (IMID).
    * Enrolled patients had a median of six prior therapies for their MM and the majority of patients (84%) were considered triple-refractory, defined as refractory to an IMID, a PI, and an anti-CD38 mAb. In addition, most (94%) had a prior

autologous stem cell transplant (auto HSCT).

* Prior treatment with a CAR-T-cell therapy and/or BCMA targeted therapy was not allowed.
* Although Abecma (idecabtagene vicleucel) is designed to target the BCMA on cancerous plasma cells, confirmation that the tumor cells were positive for this antigen was not required as a condition for inclusion in the study as it is present in the majority of MM cases.
* The primary endpoint was objective response rate (ORR) by independent review in accordance with IMWG response criteria.
* In the patients that received an infusion of idecabtagene vicleucel, an ORR of 73.4% was achieved in this uncontrolled study. Of the responses, 30.5% were stringent complete (sCR), 0.8% complete (CR), 20.3% very good partial (VGFR), and 21.9% were partial (PR).
* The median progression-free survival (PFS) and duration of response (DoR) were 8.8 months and 10.6 months, respectively, across all dosing arms.

- Subsequently, the efficacy of Abecma (idecabtagene vicleucel) was further evaluated in a randomized, open-label study [KarMMa-3] in patients with relapsed or refractory MM where it was compared with one of five standard MM therapy regimens. [34] The primary endpoint was PFS according to International Myeloma Working Group (IMWG) criteria.
  * Patients had two to four prior therapies (median of 3) which must have included Darzalex (daratumumab), an immunomodulatory agent, and a proteosome inhibitor. Disease progression must have occurred within 60 days of completing their last therapy.
  * The comparator (standard MM regimen) was chosen prior to randomization on the basis of the most recent regimen received.
  * Eighty-five percent of the patients had a prior autologous HSCT. Sixty-eight percent of the population was double-class refractory, and 66% was triple-class refractory.
  * Patients who received prior BCMA-directed therapies were excluded from the study.
  * The median PFS was 13.3 months and 4.4 months in the Abecma (idecabtagene vicleucel) and standard MM therapy treatment arms, respectively.
  * Grade 3 or 4 AEs occurred in 93% of patients in the Abecma (idecabtagene vicluecel) treatment arm and in 75% of patients in the standard therapy arm.
- Abecma (idecabtagene vicleucel) is one of several therapies directed against B-cell maturation antigen (BCMA), such as BCMA-specific bispecific T-cell engagers (BiTEs), Elrexfio (elranatamab), Tecvayli (teclistamab), or Blenrep (belantamab mafodotin). Although there is interest in the use of CAR T for MM after prior BCMA-directed therapy, there is insufficient evidence to support the use of sequential anti-BCMA therapy at this time.
- The NCCN MM guideline lists Abecma (idecabtagene vicleucel) as a category 1 treatment recommendation for MM that has progressed on or after two prior MM regimens, which must have included an anti-CD38 monoclonal antibody, an

immunomodulator agent, and a proteosome inhibitor. BCMA-specific bispecific T-cell engagers (BiTEs) [Elrexfio (elranatamab) or Tecvayli (teclistamab)] are recommended further down the treatment line, after at least four (or more) prior lines of therapy. Blenrep (belantamab mafodotin) is only available via compassionate use programs. [4]

CARVYKTI (CILTACABTAGENE AUTOLEUCEL)

Multiple Myeloma (MM):

In the single-arm CARTITUDE-1 trial, Carvykti (ciltacabtagene autoleucel) demonstrated high rates of response to therapy, including complete responses, in adults with relapsed or refractory multiple myeloma (MM).[17] Although results are promising, its effect on any long-term clinically relevant outcome is not yet known.

- The pivotal open-label CARTITUDE-1 trial enrolled 113 adult patients, who had relapsed or refractory MM, after multiple specific prior therapies. [17] However, only 97 patients received an infusion of Carvykti (ciltacabtagene autoleucel) at a dose of $0.75x10^6$ CAR-positive T cells per kilogram.
    * Subjects enrolled in the trial must have received at least 3 prior MM treatment regimens, had disease that was refractory to the most recent chemotherapy regimen, and needed to have been on an anti-CD38 monoclonal antibody (mAb), a proteosome inhibitor (PI), and an immunomodulator (IMID).
    * Enrolled patients had a median of six prior therapies for their MM and the majority of patients (88%) were considered triple-refractory, defined as refractory to an IMID, a PI, and an anti-CD38 mAb. In addition, most (98%) had a prior stem cell transplant (HSCT) [90% autologous HSCT].
    * Prior treatment with a CAR-T-cell therapy and/or BCMA targeted therapy was not allowed.
    * Although Carvykti (ciltacabtagene autoleucel) is designed to target the BCMA on cancerous plasma cells, confirmation that the tumor cells were positive for this antigen was not required as a condition for inclusion in the study as it is present in the majority of MM cases.
    * The primary endpoint was objective response rate (ORR) by independent review in accordance with IMWG response criteria.
    * In the patients that received an infusion of Carvykti (ciltacabtagene autoleucel), an ORR of 97.9% was achieved in this uncontrolled study. Of the responses, 80.4% were stringent complete (sCR), 14.4% very good partial (VGFR), and 3.1% were partial (PR).
    * The median progression-free survival (PFS) and duration of response (DoR) were 22.8 months and 21.8 months, respectively.
- The efficacy of Carvykti (ciltacabtagene autoleucel) was further evaluated in a randomized, open-label study [CARTITUDE-4] in patients with relapsed or refractory MM where it was compared with one of two standard MM therapy regimens. [35] The primary endpoint was PFS according to International Myeloma Working Group (IMWG) criteria.
    * Patients had one to three prior therapies (median of 2) which must have included an immunomodulatory agent and a proteosome inhibitor. All patients were

required to have lenalidomide-refractory disease. Only 23% of patients had disease refractory to Darzalex (daratumumab).

* Patients who received prior BCMA-directed therapies were excluded from the study.
* Additionally, patients that had MM with CNS involvement were excluded.
* The comparator (standard MM regimen) was chosen by the investigator based on prior treatment history. The choice of standard regimens included either PVd (pomalidomide/bortezomib/dexamethasone) or DPd (daratumumab/pomalidomide/dexamethasone.
* Eighty-five percent of the patients had a prior autologous HSCT. Only 15% of the population had triple-class refractory disease.
* The median PFS was not estimable and 11.8 months in the Carvykti (ciltacabtagene autoleucel) and standard MM therapy treatment arms, respectively. The hazard ratio was 0.41 [95% CI: 0.30, 0.56].

- Grade 3 or 4 AEs occurred in 97% of patients in the Carvykti (ciltacabtagene autoleucel) treatment arm and in 94% of patients in the standard therapy arm.
- Carvykti (ciltacabtagene autoleucel) is one of several therapies directed against B-cell maturation antigen (BCMA), such as BCMA-specific bispecific T-cell engagers (BiTEs), Elrexfio (elranatamab), Tecvayli (teclistamab), or Blenrep (belantamab mafodotin). Although there is interest in the use of CAR T for MM after prior BCMA-directed therapy, there is insufficient evidence to support the use of sequential anti-BCMA therapy at this time.
- The NCCN MM guideline lists Carvykti (ciltacabtagene autoleucel) as a category 1 treatment recommendation for MM that has progressed on or after <u>one</u> prior MM regimen, which must have included an immunomodulator agent and a proteosome inhibitor, and the disease is refractory to lenalidomide. BCMA-specific bispecific T-cell engagers (BiTEs) [Elrexfio (elranatamab) or Tecvayli (teclistamab)] are recommended further down the treatment line, after at least four (or more) prior lines of therapy. Blenrep (belantamab mafodotin) is only available via compassionate use programs. [4]

<u>AUCATZYL (OBECABTAGENE AUTOLEUCEL)</u>

Aucatzyl (obecabtagene autoleucel) has been studied in, and is FDA-approved for, adult patients with B-cell precursor ALL that expresses the CD19 antigen and is refractory to, or in a second or later relapse after, treatment with standard chemotherapy. [39]

B-cell precursor acute lymphoblastic leukemia (ALL):

- In a single-arm, clinical study [FELIX] Aucatzyl (obecabtagene autoleucel) demonstrated high rates of complete remission in adults with refractory or relapsed, CD19-positive, precursor B-cell ALL. [40,41]
    * Subjects had a median of two prior therapies and 34% had received a prior allogeneic stem cell transplant (ASCT). In those with a prior ASCT, more than 100 days were required to pass prior to CAR-T cell therapy administration.
    * The primary endpoint was complete remission (CR) or CR with incomplete blood recovery (CRi), which was achieved in 63% of treated patients.

    * A CR was achieved in 42% of subjects treated with Aucatzyl (obecabtagene autoleucel).
    * The MRD assay used in this trial was not analytically valid so the FDA did not allow MRD as part of the labeling for this therapy.
    * The median duration of remission was 14.1 months.
- The safety and effectiveness of Aucatzyl (obecabtagene autoleucel) has not been established in patients younger than 18 years of age. In younger patients, B-cell precursor ALL is generally considered to be a different disease with a different disease course, such that the efficacy and safety of Aucatzyl (obecabtagene autoleucel) cannot be presumed based on the available evidence from patients who are older than 18 years of age. [39]
- NCCN ALL guideline lists Aucatzyl (obecabtagene autoleucel) among several recommended options for relapsed or refractory ALL and after prior tyrosine kinases inhibitors (TKIs) if Philadelphia chromosome-positive (Ph+) ALL. [4]

PERFORMANCE STATUS

- Clinical trials of CAR T-cell therapies used Eastern Cooperative Oncology Group (ECOG) performance status (PS) as a measure of a patient's level of function and suitability for enrollment in trials.
- In clinical practice, either ECOG PS (0-1) or Karnofsky Performance Score (≥ 80) may be used to establish suitability for CAR T-cell therapy. [18]

Investigational Uses

Repeat doses of CAR-T therapy

- There is interest in the use of repeated doses of CAR T-cell therapies in patients that have resistance to or relapse after CAR T-cell infusion, including for patients with poor cell persistence. However, there is insufficient evidence currently for repeated doses of CAR T-cell therapies (see *Appendix 5*). This includes use of commercial CAR T-cell therapy products after use of CAR T-cell therapy in a clinical trial.

Use of CAR-T therapy in earlier stages of disease

- There is interest in using CAR T-cell therapies in earlier stages of disease than they were initially studied and approved. Although there are several ongoing studies that indicate they may have activity in these settings, there has also been a more critical look at the potential safety of these products, particularly surrounding their potential for causing secondary malignancies. Until a more accurate benefit versus risk is sorted out, CAR T therapies are only coverable after the number of prior lines of therapy specified in the coverage criteria.

Richter's Transformation

- There is interest in the use of CAR T-cell therapies in patients that progress to DLBCL from CLL (Richter's transformation). However, there is currently insufficient evidence to establish the safety and efficacy in Richter's transformation. Preliminary data in a small subset (n=8) at a single site is promising; however, the trial is still ongoing, and additional data is needed. [19]

Central Nervous System (CNS) lymphomas

- There is interest in the use of CAR T-cell therapies for primary CNS lymphomas. However, currently there is insufficient evidence to establish the safety and efficacy in primary CNS lymphomas.
    * *Secondary CNS lymphoma:*
        - A case series of in eight patients with secondary CNS lymphoma received Kymriah (tisagenlecleucel). [20] Two of the eight patients were treated for systemic disease, as well as CNS. Three patients had a complete response but follow up was limited (90-180 days) such that durability of response is unknown at this time.
        - In the pivotal trial for Breyanzi (lisocabtagene maraleucel) for large B cell lymphoma, seven patients had secondary CNS lymphoma, with three patients having an objective response. [9]
    * *Primary CNS lymphoma: [31]*
        - A small, uncontrolled study evaluated 12 patients who received Kymriah (tisagenlecleucel) for their relapsed or refractory primary CNS lymphoma.
        - Response was observed in 7 of the patients (6 complete responses and 1 partial response). At 12 months, 3 of 12 patients had not experienced disease progression.
- Although the available data in CNS lymphoma is promising, additional evidence is needed to establish the safety and efficacy of CAR T therapies in this setting. Use of CAR T therapies to treat CNS lymphoma is considered investigational until better information is available.
- NCCN Central Nervous System Cancers guideline does not include use of CAR T-cell therapy in primary CNS lymphoma. [4]

All Other Conditions: There is interest in using CAR T-cell therapies in other cancers, including B-cell mediated cancers that express the CD19 antigen and other leukemias and lymphomas; however, the safety and effectiveness of this therapy in diseases other than listed in the coverage criteria has not been established. [21]

Safety *[1,14,22-24,29]*

- ***Boxed Warnings:*** All currently available CAR T-cell therapy product prescribing information includes boxed warnings for cytokine release syndrome (CRS) and neurological toxicity.
    * CRS reactions may be fatal or life-threatening and may require supportive care, including admission to an intensive care unit (ICU). Package labeling has a box warning describing this risk.
    * CAR T-cell therapies are only available through restricted programs under a Risk Evaluation and Mitigation Strategy (REMS) and are only infused at authorized treatment centers.
    * The box warnings also describe a risk of serious and potentially fatal or life-threatening neurological toxicities, including seizures (risk varies with product. See full prescribing information for details).

- *Additional Abecma Boxed Warnings:* Hemophagocytic lymphohistiocytosis/ macrophage activation syndrome (HLH/MAS) and prolonged cytopenia with bleeding and infection.
- Additional warnings and precautions include hypersensitivity reactions (premedication is recommended prior to administration), serious infections, hypogammaglobulinemia (the need for life-long immune globulin is possible), prolonged cytopenias, development of secondary malignancies, and decreased ability to drive and operate machinery for at least eight weeks after infusion of CAR-T therapies. See full prescribing information for additional details.
- Treatment with CAR T-cell therapy is only available through select treatment centers authorized by the respective manufacturers.
    * Kymriah: Refer to https://www.us.kymriah.com/acute-lymphoblastic-leukemia-children/interested-in/where-to-get-treatment/
    * Tecartus: Refer to https://www.tecartus.com/treatment-center-locator
    * Yescarta: Refer to https://www.yescarta.com/find-a-treatment-center/
    * Breyanzi: Refer to https://www.breyanzi.com/treatment-centers/
    * Abecma: Refer to https://www.abecma.com/find-a-treatment-center/
    * Carvykti: https://www.carvyktihcp.com/treatment-centers
    * Aucatzyl: https://www.aucatzylhcp.com/atc-locator/
- In some regions, site of care may be further limited by insurance providers.

Appendix 1:

Tyrosine Kinase Inhibitors (TKIs) Indicated for Philadelphia chromosome-Positive B-Cell Acute Lymphoblastic Leukemia (ALL) [4]	
Iclusig (ponatinib)	(dasatinib (generic, Sprycel)
imatinib (generic, Gleevec)	

Appendix 2:

Response (Remission) Definitions for ALL [4]
Blood and Bone Marrow:
Complete response (CR): - No circulating blasts or extramedullary disease - Trilineage hematopoiesis (TLH) and < 5% blasts - Absolute neutrophil count (ANC) > 1000/microliter - Platelets > 100,000/microliter - No recurrence for 4 weeks ***Complete response with incomplete blood count recovery (CRi):*** - Meets all criteria above for a complete response except for platelet count and/or ANC ***The overall response rate (ORR) includes both CR and CRi [ORR = CR + CRi]***
CNS remission:
No lymphoblasts in CSF regardless of WBC count
Lymphomatous Extramedullary Disease:
CR: Complete resolution of lymphomatous enlargement by CT scan of neck, chest, abdomen, and pelvis with IV contrast. (If previous positive PET scan, a post-treatment residual mass of any size is considered a complete response if it is PET negative)

Appendix 3:

Bruton's Tyrosine Kinase (BTK) Inhibitors Indicated for Mantle-Cell Lymphoma (MCL) and Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL) [4]	
Brukinsa (zanubrutinib)	Imbruvica (ibrutinib)
Calquence (acalabrutinib)	Jaypirca (pirtobrutinib)

Appendix 4:

Select Therapies Indicated for Multiple Myeloma (MM) [4]	
Anti-CD38 Monoclonal Antibodies	
daratumumab (Darzalex, Darzalex Faspro)	Sarclisa (isatuximab)
Proteosome Inhibitors	
bortezomib (generics, Velcade) Kyprolis (carfilzomib)	Ninlaro (ixazomib)
Immunomodulatory Agents	
lenalidomide (generics, Revlimid) Pomalyst (pomalidomide)	Thalomid (thalidomide)

Appendix 5:

Gene Therapies – CAR T [1,14,22-24,29]									
Coverable diagnoses, by CAR T product [f]	**B-cell ALL**	**Large B-cell lymphoma, or a related lymphoma diagnosis**				**FL**	**MCL**	**MM**	CLL/ SLL
		DLBCL	**High-grade B-cell lymphoma**	**DLBCL arising from FL (transformed FL)**	**PMBCL**				
Abecma, idecabtagene vicleucel								√	
Aucatzyl, obecabtagene autoleucel	√								
Carvykti, ciltacabtagene autoleucel								√ [g]	
Breyanzi, lisocabtagene maraleucel		√	√	√	√	√	√		√
Kymriah, tisagenlecleucel	√	√	√	√		√			
Tecartus, brexucabtagene autoleucel	√						√		
Yescarta, axicabtagene ciloleucel		√	√	√	√	√			

ALL: acute lymphoblastic leukemia; DLBCL: diffuse large B-cell lymphoma; CLL: Chronic lymphocytic leukemia; FL: follicular lymphoma; MCL: Mantle cell lymphoma; MM: Multiple myeloma; PMBCL: Primary mediastinal large B-cell lymphoma; SLL: Small lymphocytic lymphoma

[f] This chart is subject to change at any time, given the rapid evolution of evidence as well as FDA-approval status. Any new FDA approvals not in this policy would be subject to the "New To Market Drugs and Indications" policy dru517

[g] Based on available evidence

Cross References
BlueCross BlueShield Association Medical Policy, 8.01.63 - Chimeric Antigen Receptor Therapy for Leukemia and Lymphoma [January 2024]
BlueCross BlueShield Association Medical Policy, 8.01.66 - Chimeric Antigen Receptor Therapy for Multiple Myeloma [April 2023]
Adoptive Immunotherapy, BlueCross BlueShield Association Medical Policy 8.01.01 [November 2023]
Drugs for chronic inflammatory diseases, Medication Policy Manual, Policy No. dru444
Acute lymphoblastic leukemia (ALL)
Besponsa, inotuzumab ozogamicin, Medication Policy Manual, Policy No. dru529
Blincyto, blinatumomab, Medication Policy Manual, Policy No. dru388
Iclusig, ponatinib, Medication Policy Manual, Policy No. dru292
dasatinib (generic, Sprycel), Medication Policy Manual, Policy No. dru137
Chronic lymphocytic leukemia (CLL) and Small lymphocytic lymphoma (SLL)
Bruton's tyrosine kinase (BTK) inhibitors, Medication Policy Manual, Policy No. dru691
Gazyva, Obinutuzumab, Medication Policy Manual, Policy No. dru327
PI3K inhibitors, Medication Policy Manual, Policy No. dru706
Venclexta, venetoclax, Medication Policy Manual, Policy No. dru462
Large B-cell lymphoma
Bispecific T-cell Engager (BiTE) Therapies for B-cell Lymphoma, Medication Policy Manual, Policy No. dru761
Products with Therapeutically Equivalent Biosimilars/Reference Products, Medication Policy Manual, Policy No. dru620
Monjuvi-cxix, tafasitamab, Medication Policy Manual, Policy No. dru652
Polivy-piiq, polatuzumab vedotin, Medication Policy Manual, Policy No. dru600
Zynlonta, loncastuximab tesirine-lpyl, Medication Policy Manual, Policy No. dru675
Mantle-cell lymphoma
Bruton's tyrosine kinase (BTK) inhibitors, Medication Policy Manual, Policy No. dru691
Multiple Myeloma
Medications for Multiple Myeloma, other cancers, and other hematologic disorders, Medication Policy Manual, Policy No. dru672

Codes	Number	Description
Abecma (idecabtagene vicleucel)		
HCPCS	Q2055	Idecabtagene vicleucel, up to 460 million autologous b-cell maturation antigen (bcma) directed car-positive t cells, including leukapheresis and dose preparation procedures, per therapeutic dose
Aucatzyl (obecabtagene autoleucel)		
HCPCS	N/A	Not available
Breyanzi (lisocabtagene maraleucel)		
HCPCS	Q2054	Lisocabtagene maraleucel, up to 110 million autologous anti-cd19 car-positive viable t cells, including leukapheresis and dose preparation procedures, per therapeutic dose
Carvykti (ciltacabtagene autoleucel)		
HCPCS	Q2056	Ciltacabtagene autoleucel, up to 100 million autologous b-cell maturation antigen (bcma) directed car-positive t cells, including leukapheresis and dose preparation procedures, per therapeutic dose
Kymriah (tisagenlecleucel)		
HCPCS	Q2042	Tisagenlecleucel (Kymriah), up to 250 million car-positive viable t-cells, including leukapheresis and dose preparation procedures, per infusion
Tecartus (brexucabtagene autoleucel)		
HCPCS	Q2053	Brexucabtagene autoleucel, up to 200 million autologous anti-cd19 car positive viable t cells, including leukapheresis and dose preparation procedures, per therapeutic dose
Yescarta (axicabtagene ciloleucel)		
HCPCS	Q2041	Axicabtagene ciloleucel (Yescarta), up to 200 million autologous anti-cd19 car positive viable t cells, including leukapheresis and dose preparation procedures, per therapeutic dose

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Revision History

Revision Date	Revision Summary
3/6/2025	Effective 4/15/25: • Added coverage for Aucatzyl (oxecabtagene autoleucel) for relapsed or refractory CD19-postive, B-cell acute lymphocytic leukemia (B-ALL). • Coverage is identical to the other two CAR T therapies approved for B-ALL. (Aucatzyl was added to the coverage table for Kymriah and Tecartus under criterion 1).
9/19/2024	• Expanded coverage of Breyanzi (lisocabtagene maraleucel) based on new evidence and new FDA indications. Added coverage criteria for the following: • Relapsed or refractory chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) after at least three prior therapies for disease with standard risk disease (no high-risk cytogenetics). Prior therapy must have included a BTK inhibitor-based regimen and a Venclexta (venetoclax)-based regimen in each population. • Relapsed or refractory follicular lymphoma (FL) after at least two prior therapies.

Revision Date	Revision Summary
	• Relapsed or refractory mantle cell lymphoma (MCL) after at least two prior therapies.
6/20/2024	• Updated criteria for Abecma (idecabtagene vicleucel) in multiple myeloma (MM) based on new evidence which led to an expanded indication. Coverage was modified from 'at least four prior therapies' to 'at least two prior MM regimens including an immunomodulatory agent, a proteosome inhibitor, and an anti-CD38 monoclonal antibody'. • Updated criteria for Carvykti (ciltacabtagene autoleucel) in MM based on new evidence which led to an expanded indication. Coverage was modified from 'at least four prior therapies' to 'at least one prior MM regimen including an immunomodulator agent and a proteosome inhibitor, AND is refractory to lenalidomide'.
3/21/2024	No criteria changes with this annual review.
3/16/2023	• No changes to coverage criteria with this annual update. • Appendices were updated (no change to policy intent).
9/23/2022	• Added coverage criteria for Kymriah (tisagenlecleucel) in the third- and subsequent-line FL setting. • Added coverage criteria for Breyanzi (lisocabtagene maraleucel) in the second-line DLBCL setting, when certain criteria are met, a newly FDA approved indication.
6/17/2022	Added coverage criteria for Yescarta (axicabtagene ciloleucel) in the second-line DLBCL setting, when certain criteria are met, a newly FDA approved indication.
3/18/2022	• Formatted coverage criteria in tabular format to simplify review (no change to intent of policy). • Simplified criteria for "suitable ("fit") for CAR T therapy." Removed criteria requiring not eligible for a clinical trial, need to be enrolled in a health plan care management program, and absence of GVHD. • Added "Repeat doses of CAR T-cell therapy" to the list of Investigational Uses (no change to intent of coverage). • Added brand name for ciltacabtagene autoleucel, Carvykti. Product is now FDA-approved.
10/15/2021	• Added coverage criteria for ciltacabtagene autoleucel, a new CAR-T product under FDA review, for patients with relapsed or refractory multiple myeloma. • Added coverage criteria for Tecartus (brexucabtagene autoleucel) in adult patients with acute lymphoblastic leukemia (ALL), a newly FDA approved indication.

Revision Date	Revision Summary
7/16/2021	• Added the newly FDA-approved Abecma (idecabtagene vicleucel) to policy. Limits coverage to patients with relapsed or refractory multiple myeloma when certain criteria are met. • Added coverage criteria for Yescarta (axicabtagene ciloleucel) in patients with follicular lymphoma when certain criteria are met, a newly FDA approved indication. • Updated coverage criteria for patients with diffuse large B-cell lymphoma (DLBCL) and secondary CNS lymphoma.
4/22/2021	• Updated policy background section and updated lisocabtagene maraleucel with its final product name, Breyanzi, where applicable. • Updated coverage criteria to allow coverage of Breyanzi in PMBCL, • Clarified coverage criteria for patient suitability for CAR T-cell therapy, including the need for recent clinical documentation, performance status (use of ECOG or KPS), enrollment in to care management, and clinical trial (provider attestation).
10/28/2020	Updated policy background section and updated KTE-X19 with its final product name, Tecartus (brexucabtagene autoleucel), where applicable. No change to intent of policy.
7/22/2020	Added coverage criteria for lisocabtagene maraleucel (liso-cel) and KTE-X19, two new CAR-T products under FDA review (effective 9/1/2020).
6/15/2020	Removed references to brand Rituxan from policy to account for upcoming changes in biosimilars policy (dru620).
4//22/2020	• Added continuation of therapy (COT) criteria (no change to intent of coverage criteria). • Added criteria III.A.6, referencing ineligibility for clinical trial enrollment. • Updated evidence for the use with CNS lymphoma (Investigational).
11/16/2018	Lymphoma coverage criterion (II.B.2.c) was modified to state that a contraindication to coverage is active CNS disease.
9/21/2018	Added coverage of tisagenlecleucel in DLBCL, a new indication.
3/19/2018	New policy.

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Medication Policy Manual | **Policy No:** dru527

Topic: Luxturna, voretigene neparvovec-rzyl | **Date of Origin:** August 1, 2018

Committee Approval Date: March 21, 2024 | **Next Review Date:** 2025

Effective Date: June 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Luxturna (voretigene neparvovec-rzyl) is a gene therapy used for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy.

Policy/Criteria

Most contracts require pre-authorization approval of Luxturna (voretigene neparvovec-rzyl) prior to coverage.

I. Luxturna (voretigene neparvovec-rzyl) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) confirming that criteria A through E below are met.

A. A diagnosis of biallelic RPE65 mutation-associated retinal dystrophy confirmed by genetic testing.

AND

B. There are sufficient viable retinal cells (defined an area of retinal thickness>100 microns within the posterior pole), as measured by optical coherence tomography (OCT).

AND

C. The member is at least 12 months of age.

AND

D. The member has remaining light perception in the eye or eyes that will receive treatment.

AND

E. The member has not had any of the following:

1. Prior intraocular surgery within 6 months.

2. Use of high-dose (>7500 retinol equivalent units [or >3300 IU] per day of vitamin A) retinoid compounds in the past 18 months.

II. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Luxturna (voretigene neparvovec-rzyl) coverable only under the medical benefit (as a provider-administered medication).

B. When preauthorization is approved, Luxturna (voretigene neparvovec-rzyl) will be authorized in quantities of one dose per eye per lifetime.

III. Luxturna (voretigene neparvovec-rzyl) is considered investigational when:

A. Used as re-treatment.

B. Used for inherited retinal diseases not due to an RPE65 mutation.

C. Used after or in combination with any other gene therapy.

Position Statement

- Luxturna (voretigene neparvovec-rzyl) is indicated for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy. Patients must have viable retinal cells as determined by the treating physician(s). [1]
- Inherited retinal dystrophies (IRDs) are a diverse group of disorders with overlapping phenotypes characterized by progressive degeneration and dysfunction of the retina.[2]
- Biallelic RPE65 mutation-associated retinal dystrophy is a rare genetic condition and encompasses several clinical diagnoses, including Leber congenital amaurosis (LCA), Retinitis Pigmentosa (RP), and Severe Early Childhood Onset Retinal Dystrophy (SECORD).
- Genetic testing is required to confirm the diagnosis of RPE65-mediated retinal dystrophy.
- Luxturna (voretigene neparvovec-rzyl) is given as sequential, bilateral subretinal injections of 1.5E11 (or 150 billion) vg delivered in a total subretinal volume of 0.3 mL per eye. The individual procedures to each eye are performed on separate days no more than 6 days apart. The procedure is given under general anesthesia.
- Use of Luxturna (voretigene neparvovec-rzyl) is limited to medical centers with retina specialists with expertise in inherited retinal disorders, vitreoretinal surgery expertise, and pharmacies adequately trained to handle the product.
- Luxturna (voretigene neparvovec-rzyl) has been shown to improve visual function in low light settings, as measured by the multi-luminance mobility test (MLMT).
- In clinical studies, patients who had more advanced disease, did not experience improvement.
- Use in infants under 12 months of age is not recommended because of potential dilution or loss of Luxturna (voretigene neparvovec-rzyl) after administration due to active retinal cells proliferation.
- Luxturna (voretigene neparvovec-rzyl) has only been studied for inherited retinal dystrophies due to biallelic RPE65 mutations. There is no evidence for inherited retinal diseases due to other mutations.
- Repeated doses of Luxturna (voretigene neparvovec-rzyl) have not been studied. In clinical studies, patients received one dose in each eye once.
- Luxturna (voretigene neparvovec-rzyl) has not been studied after or in combination with other gene therapies.

Clinical Efficacy

- The efficacy of Luxturna (voretigene neparvovec-rzyl) was evaluated in one open-label, randomized, controlled, phase 3 trial. [3 4]
    * Patients with a confirmed diagnosis of RPE65-mediated retinal dystrophy were randomized 2:1 to receive Luxturna (voretigene neparvovec-rzyl) or to a control group.
    * The study excluded patients who had used high-dose (>7500 retinol equivalent units [or >3300 IU] per day of vitamin A) retinoid compounds in the past 18 months or who had intraocular surgery in the past 6 months.

* The primary endpoint was change in multi-luminance mobility test (MLMT) score at 1 year.
    - The MLMT was designed to measure functional vision and integrate aspects of visual acuity, visual field, and light sensitivity. To complete the MLMT patients navigate a marked path in varying light levels. The path contained various obstacles that subjects must navigate around. Patients successfully completed the MLMT if they completed the course in less than 3 minutes with less than 4 errors.
    - An improvement in score at one year meant that patients could complete the course at a lower light level than at baseline.
* The mean of the bilateral MLMT change score at one year was 1.8 in the intervention group and 0.2 in the control group (a difference of 1.6; 95% CI 0.72 to 2.41, p = 0.0013).
* Three patients who could not complete the MLMT at the brightest light level at baseline did not experience improvement after one year. Patients with more advanced disease may be less likely to have improvement in visual function.
* Key secondary endpoints included full-field light sensitivity threshold testing (FST) and best corrected visual acuity (BCVA).
    - In the intervention group, mean FST showed improvement in light sensitivity by day 30 and remained stable over 1 year. The control group showed no meaningful change in this measure over 1 year.
    - Results for BCVA favored the treatment group, but were not statistically significant.
* While Luxturna (voretigene neparvovec-rzyl) provides a significant therapeutic advance which may provide improvement in vision, it is not expected to restore normal vision, and longer-term clinical evidence is pending, to understand the durability of response.
    - A systematic review found that for improvements in BCVA and FST, voretigene neparvovec was effective up to 2 years post treatment. However, the improvement in BCVA was not sustainable and the data were not available in FST sensitivity beyond 2 years post treatment. [5]

Diagnosis

- Genetic testing is required to establish a diagnosis of RPE65 mediated retinal dystrophy. Pathogenic variant(s) must be present in both copies of the RPE65 gene to establish a diagnosis of biallelic RPE65-mediated inherited retinal dystrophy. Clinical studies included patients with pathogenic variations in the homozygous or compound heterozygous state. [1 6]

Investigational Uses

- Retreatment with Luxturna (voretigene neparvovec-rzyl) has not been studied. Additional studies and clinical experience with Luxturna (voretigene neparvovec-rzyl) are needed to determine the role of retreatment and to identify safety and efficacy with repeat dosing. [3]

- Luxturna (voretigene neparvovec-rzyl) has not been studied in patients with inherited retinal dystrophies due to mutations other than biallelic RPE65 mutations.

Cross References
BlueCross BlueShield Association Medical Policy, 2.04.144 - Gene Therapy for Inherited Retinal Dystrophy. [February 2023]

Codes	Number	Description
HCPCS	J3398	Injection, voretigene neparvovec-rzyl (Luxturna), 1 billion vector genomes

References

1. Luxturna [Prescribing information]. Philadelphia, PA: Spark Therapeutics; May 2022
2. Hartong DT, Berson EL,Dryja TP. Retinitis pigmentosa. Lancet. England, 2006:1795-809.
3. U.S. Food and Drug Administration. Advisory committee briefing document on Voretigene Neparvovec (BLA 125610). [cited 11/06/2017]; Available from: https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/CellularTissueandGeneTherapiesAdvisoryCommittee/UCM579290.pdf.
4. Russell S, Bennett J, Wellman JA, et al. Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65-mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial. *Lancet.* 2017;390(10097):849-60. PMID: 28712537
5. Wang X, Yu C,Tzekov R. The effect of human gene therapy for RPE65-associated Leber's congenital amaurosis on visual function: a systematic review and meta-analysis. *Orphanet J Rare Dis.* 2019;15(49 (2020):https://doi.org/10.1186/s13023-020-1304-1.
6. Food and Drug Administration, Voretigene neparvovec BLA Clinical Review: https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM592766.pdf. Accessed: 6/1/2018

Revision History

Revision Date	Revision Summary
3/21/2024	No criteria changes with this annual review.
3/16/2023	No changes to coverage criteria with this annual update.
3/18/2022	No changes to coverage criteria with this annual update.
4/21/2021	No changes to coverage criteria with this annual update.
10/28/2020	Removed COT language, as it is not applicable for a medication dosed such as Luxturna (voretigene neparvovec-rzyl).
4/22/2020	Added continuation of therapy language (no change to intent of coverage criteria).
10/23/2019	No changes to coverage criteria with this annual update.
7/20/2018	New Policy, effective on August 1, 2018.

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Medication Policy Manual | **Policy No:** dru529

Topic: Besponsa, inotuzumab ozogamicin | **Date of Origin:** March 1, 2018

Committee Approval Date: March 21, 2023 | **Next Review Date:** 2025

Effective Date: June 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Besponsa (inotuzumab ozogamicin) is an intravenously infused antibody-drug conjugate medication. It delivers cytotoxic chemotherapy to malignant B-cells, thereby causing cell death. It is approved for the treatment of adults with B-cell precursor acute lymphoblastic leukemia (ALL).

Policy/Criteria

Most contracts require pre-authorization approval of Besponsa (inotuzumab ozogamicin) prior to coverage.

I. Continuation of therapy (COT): Besponsa (inotuzumab ozogamicin) may be considered medically necessary for COT when criteria A, B, or C **AND** D below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

AND

D. The requested number of doses (cycles) is within the policy limits below (Note: Doses (cycles) already administered will be counted towards the coverable maximum quantity).

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Besponsa (inotuzumab ozogamicin) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes), that criteria A through E below are met.

A. A diagnosis of **relapsed or refractory B-cell acute lymphoblastic leukemia** (ALL).

AND

B. There is documentation providing current confirmation of CD22 tumor expression.

AND

C. The patient has received prior therapy meeting criteria 1 and 2 below:

1. At least one prior cytotoxic chemotherapy induction regimen has been ineffective.

AND

2. If the ALL is positive for the Philadelphia chromosome (Ph-positive), at least one tyrosine kinase inhibitor (TKI) indicated for ALL was not effective, unless all are contraindicated or not tolerated.

AND

D. The patient does not have active central nervous system (CNS) leukemia.

AND

E. When either criterion 1 or 2 is met:

1. Besponsa (inotuzumab ozogamicin) will be used as a monotherapy.

OR

2. Besponsa (inotuzumab ozogamicin) will be used in combination with a mini-hyperCVD (cyclophosphamide, dexamethasone, vincristine, methotrexate, and cytarabine) regimen in relapsed or refractory Ph-negative ALL.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Besponsa (inotuzumab ozogamicin) coverable only under the medical benefit (as a provider-administered medication).

B. **Initial authorization:** When pre-authorization is approved, up to nine doses (three cycles) of Besponsa (inotuzumab ozogamicin) will be authorized over a three-month period.

C. **Continued authorization:** In patients who achieve a complete remission but who are not proceeding to a hematopoietic stem cell transplant (HSCT), up to nine additional doses (three additional cycles) will be authorized in a consecutive three-month period. No doses beyond a total of six-cycles will be authorized.

IV. Besponsa (inotuzumab ozogamicin) is considered investigational when:

A. Used in combination with other ALL therapies.

B. Used in quantities exceeding the number of doses listed above.

C. Use after hematopoietic stem cell transplant (HSCT), including use of doses pre-authorized for administration prior to HSCT, but given after HSCT.

D. Used for all other conditions.

Position Statement

Summary

- Besponsa (inotuzumab ozogamicin) is an intravenously infused antibody-drug conjugate that targets the CD22 antigen on B-cells. It delivers a cytotoxic chemotherapy agent that causes cell death. It was studied and subsequently approved for the treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).
- Intent of the policy is to cover Besponsa (inotuzumab ozogamicin) for B-cell precursor ALL when standard chemotherapy is ineffective, the setting where its safety and effectiveness has been studied.
- Besponsa (inotuzumab ozogamicin) was studied in adult patients with CD22-positive B-cell ALL that had relapsed after, or was refractory to, induction with a standard chemotherapy regimen who were scheduled for their first- or second salvage therapy. For Philadelphia chromosome-positive (Ph+) disease, patients were unresponsive to both standard induction therapy and a tyrosine kinase inhibitor indicated for Ph+ ALL.
- Patients with active central nervous system (CNS) leukemia were not included in the pivotal clinical study.
- Approval of Besponsa (inotuzumab ozogamicin) was based on its ability to induce a complete remission relative to investigator's choice of chemotherapy. The remission rates were 80% and 29%, respectively. However, there was no difference in median overall survival between the two groups.
- The National Comprehensive Cancer Network (NCCN) acute lymphoblastic lymphoma guideline Besponsa (inotuzumab ozogamicin) among category 1 recommendations for patients with Ph-negative relapsed or refractory ALL. It is listed as a category 2A recommendation for those with Ph-positive relapsed or refractory ALL.
- Besponsa (inotuzumab ozogamicin) is administered as a 60-minute infusion on Days 1, 8, and 15 of each cycle (the initial cycle is 21 days, subsequent cycles are 28 days). The dose is dependent of the response achieved after cycle 1, and may be adjusted based on side effects. It may be given for a maximum of six cycles in patients who do not receive a hematopoietic stem cell transplant (HSCT).
- Besponsa (inotuzumab ozogamicin) has not been studied for use after hematopoietic stem cell transplant.
- Besponsa (inotuzumab ozogamicin) labeling carries a BOX WARNING describing the potential for liver toxicity, including veno-occlusive disease, and an increase in post bone marrow transplant mortality.
- There is possible interest in using Besponsa (inotuzumab ozogamicin) in other B-cell lymphomas; however, there is currently no published evidence evaluating the safety and effectiveness of this medication in these conditions.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.

- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy

- The approval of Besponsa (inotuzumab ozogamicin) was based on an open-label RCT that compared it with investigator's choice of chemotherapy in patients who relapsed after or were refractory to a front-line chemotherapy regimen. [1]
    - Patients enrolled in the study had CD22-positive ALL (included both Philadelphia chromosome (Ph)-positive and Ph-negative patients).
    - Complete remission, the primary endpoint, was achieved by 80.7% and 29.4% of subjects in the Besponsa (inotuzumab ozogamicin) and chemotherapy arms, respectively.
    - The median duration of response was 4.6 months and 3.1 months in the Besponsa (inotuzumab ozogamicin) and chemotherapy arms, respectively. However, no difference in overall survival was detected between the two therapies.
- Although it appears Besponsa (inotuzumab ozogamicin) has activity in patients with relapsed or refractory B-cell ALL based on its ability to induce disease remission, the small difference in duration of response and the lack of improvement in overall survival relative to chemotherapy brings into question the overall clinical benefit of this therapy.
- The National Comprehensive Cancer Network (NCCN) acute lymphoblastic leukemia (ALL) guideline lists Besponsa (inotuzumab ozogamicin) as a category 1 recommendation for Ph-negative ALL. Blincyto (blinatumomab) is also listed as a category 1 recommendation in this population. Besponsa (inotuzumab ozogamicin) is also listed among several category 2A recommendations for patients with Ph-positive ALL. In patients with relapsed or refractory Ph-negative ALL, use of Besponsa (inotuzumab ozogamicin) in combination with mini-hyperCVD (cyclophosphamide, dexamethasone, vincristine, methotrexate, and cytarabine) is listed as a category 2a.[2]

Investigational Uses

- Based on its mechanism of action, Besponsa (inotuzumab ozogamicin) may have potential applications in other B-cell-mediated cancers; [3] however, there is currently no published evidence supporting use in any condition other than CD22-positive B-cell ALL.
- NCCN guidelines do not list Besponsa (inotuzumab ozogamicin) as a treatment option outside of the relapsed or refractory B-cell ALL setting.

Safety [4,5]

- Current safety experience with Besponsa (inotuzumab ozogamicin) is limited. However, there are significant adverse effects associated with its use that have been identified in the clinical trial. It delivers the same cytotoxic chemotherapy agent to cells as Mylotarg (gemtuzumab ozogamicin), which was withdrawn from the market for several years due to deaths associated with hepatic veno-occlusive disease (VOD).
- Besponsa (inotuzumab ozogamicin) and Mylotarg (gemtuzumab ozogamicin) carry BOX WARNINGS for hepatotoxicity, including hepatic VOD and increased risk of post-hematopoietic stem cell transplant non-relapse mortality.

Dosing [4]

- Premedication with corticosteroids, antipyretics, and antihistamines is recommended prior to each Besponsa (inotuzumab ozogamicin) infusion.
- Besponsa (inotuzumab ozogamicin) is given via a 60-minute infusion on Days 1, 8, and 15 of each cycle. The initial cycle is 21 days. Subsequent cycles are 28 days in length. Dosing is based on body surface area.
- For patients proceeding to a hematopoietic stem cell transplant, the recommended duration of therapy is two cycles. A third cycle may be given if the patient does not achieve a complete remission and minimal residual disease (MRD) negativity after two cycles.
- A maximum of six cycles of treatment may be administered to patients who are not proceeding to hematopoietic stem cell transplant.

Appendix 1: Tyrosine Kinase Inhibitors (TKIs) Indicated for Philadelphia chromosome-Positive B-Cell Acute Lymphoblastic Leukemia (ALL)
Iclusig (ponatinib)
Gleevec (imatinib)
Sprycel (dasatinib)

Cross References
Sprycel, dasatinib, Medication Policy Manual, Policy No. dru137
Iclusig, ponatinib, Medication Policy Manual, Policy No. dru292
Blincyto, blinatumomab, Medication Policy Manual, Policy No. dru388
Chimeric Antigen Receptor (CAR) T-cell Therapies, Medication Policy Manual, Policy No. dru523

Codes	Number	Description
HCPCS	J9229	Injection, inotuzumab ozogamicin (Besponsa), 0.1 mg

References

1. Kantarjian, HM, DeAngelo, DJ, Stelljes, M, et al. Inotuzumab Ozogamicin versus Standard Therapy for Acute Lymphoblastic Leukemia. *N Engl J Med*. 2016 Aug 25;375(8):740-53. PMID: 27292104
2. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. [Updated routinely]. [cited with policy updates and as necessary]. Available from: https://www.nccn.org/guidelines/category_1
3. National Institutes of Health, Clinicaltrials.gov [website]. [cited periodically]; Available from: www.clinicaltrials.gov
4. Besponsa (inotuzumab ozogamicin) package insert. Philadelphia, PA: Wyeth Pharmaceuticals Inc; A subsidiary of Pfizer, Inc.; March 2018.
5. Mylotarg (gemtuzumab ozogamicin) package insert. Philadelphia, PA: Wyeth Pharmaceuticals Inc; A subsidiary of Pfizer, Inc.; September 2017.

Revision History

Revision Date	Revision Summary
3/21/2024	No criteria changes with this annual review.
3/16/2023	No criteria changes with this annual review.
3/18/2022	No criteria changes with this annual review.
4/21/2021	Updated continuation of therapy (COT) criteria. No other updates with this annual review.
4/22/2020	• Added continuation of therapy (COT) criteria. • Updated coverage criteria E. to allow Besponsa (inotuzumab ozogamicin) in combination with mini-hyperCVD (cyclophosphamide, dexamethasone, vincristine, methotrexate, and cytarabine) in patients with relapsed or refractory Ph-negative ALL.
2/16/2018	New policy.

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Medication Policy Manual | **Policy No:** dru530

Topic: Mylotarg, gemtuzumab ozogamicin | **Date of Origin:** March 1, 2018

Committee Approval Date: September 19, 2024 | **Next Review Date:** 2025

Effective Date: December 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Mylotarg (gemtuzumab ozogamicin) is an intravenously infused antibody-drug conjugate medication. It delivers cytotoxic chemotherapy to myeloid cells that express the CD33 antigen, thereby causing cell death. It is approved for the treatment of CD33-positive acute myeloid leukemia (AML).

Policy/Criteria

I. Continuation of therapy (COT): Mylotarg (gemtuzumab ozogamicin) may be considered medically necessary for COT criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Mylotarg (gemtuzumab ozogamicin) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A and B below are met.

A. A diagnosis of **CD33-positive acute myeloid leukemia** (AML) in one of the following settings (1 or 2):

1. Adult or pediatric patients (1 month of age and older) naïve to prior AML treatment.

OR

2. Adult or pediatric patients (2 years of age and older) with disease that relapsed after, or was refractory to, a prior AML induction chemotherapy regimen.

AND

B. The patient does not have active central nervous system (CNS) leukemia.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Mylotarg (gemtuzumab ozogamicin) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Mylotarg (gemtuzumab ozogamicin) will be approved in the following quantities:

Table 1:

Treatment setting:	**Maximum number of infusions:**
Adults with newly diagnosed AML when used in combination with chemotherapy	Up to five infusions
Pediatric patients with newly diagnosed AML when used in combination with chemotherapy	Up to two infusions
Adults with newly diagnosed AML when used as a single agent	Up to ten infusions
Adults or pediatric patients with relapsed or refractory AML	Up to three infusions

C. **Continued Authorization:** No additional doses of Mylotarg (gemtuzumab ozogamicin) will be authorized.

IV. Mylotarg (gemtuzumab ozogamicin) is considered investigational when:

A. Used in quantities exceeding the maximum number of infusions listed in the Quantity Limits above (*Table 1).*

B. Used for all other conditions.

Position Statement

Summary

- Mylotarg (gemtuzumab ozogamicin) is an intravenously infused antibody-drug conjugate that targets the CD33 antigen present on myeloid cells. It delivers a cytotoxic chemotherapy agent that causes cell death. It was studied and subsequently approved for newly diagnosed CD33-positive (CD33+) acute myeloid leukemia (AML) in adults, and in relapsed or refractory CD33+ AML in adults and pediatrics (≥ 2 years of age).
- The intent of this policy is to cover Mylotarg (gemtuzumab ozogamicin) for the indications and regimen for which it has been shown to be safe and effective, as detailed in the coverage criteria.
- Mylotarg (gemtuzumab ozogamicin) initially received FDA Accelerated approval in 2000 but was withdrawn from the market in 2010 because clinical benefit (survival) had not yet been established despite the completion of several follow-on phase 3 trials. Post-marketing experience also revealed a significant risk of fatal hepatic veno-occlusive disease (VOD) suggesting that risks with this medication were greater than potential benefit.
- The re-approval of Mylotarg (gemtuzumab ozogamicin) in late 2017 is based on four pivotal studies in various populations and settings. Although it appears to have activity in AML based on induction of disease remission, an initial goal of therapy, a clear long-term clinical benefit has not yet been established (e.g., improved survival or quality of life).
    * ***Adults with newly diagnosed CD33+ AML:***
        - There was no difference in remission rates in patients receiving chemotherapy alone, versus chemotherapy plus Mylotarg (gemtuzumab ozogamicin). There was no difference in overall survival (OS) at 2 years after adjustment for factors of prognostic importance.
        - A statistically significant, but not likely a clinically relevant, difference in median OS (five weeks) was noted with Mylotarg (gemtuzumab ozogamicin) relative to best supportive care.
    * ***Adults with CD33+ AML in first relapse:*** Remission rates of 26% were reported in a small observational study. Long term clinical benefits, and relative comparisons to other therapies or best supportive care are not known.
    * ***Pediatric patients with relapsed or refractory CD33+ AML:*** Use in pediatrics in based on a small (28 patient) observational study in children ages 2 to 18 years and a retrospective literature review of case studies in which it was noted that there were no differences in efficacy or safety observed by age.
- Patients with active central nervous system (CNS) leukemia were not included in the pivotal clinical studies so it is not known if it provides any benefit in this population.
- The National Comprehensive Cancer Network (NCCN) AML guideline lists Mylotarg (gemtuzumab ozogamicin) as a treatment option for its labeled indications.

- Mylotarg (gemtuzumab ozogamicin) is administered as a 120-minute infusion. The dose and schedule are determined by the disease setting and whether it is administered as an add-on to a chemotherapy regimen, or as a single agent *(refer to Dosing section of policy).*
- Mylotarg (gemtuzumab ozogamicin) labeling carries a BOX WARNING describing the potential for liver toxicity, including severe or fatal VOD.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy

- Mylotarg (gemtuzumab ozogamicin) initially received FDA Accelerated approval in 2000 but was withdrawn from the market in 2010 because clinical benefit (survival) had not yet been established despite the completion of several follow-on phase 3 trials. Post-marketing experience also revealed a significant risk of fatal hepatic veno-occlusive disease (VOD) suggesting that risks with this medication were greater than potential benefit. [1]
- The current approval (late 2017) of Mylotarg (gemtuzumab ozogamicin) was based on four pivotal trials in the following settings:
    * ***Adults with newly diagnosed AML with Mylotarg (gemtuzumab ozogamicin) as an add-on to chemotherapy:*** [2]
        - This study compared chemotherapy alone with chemotherapy plus Mylotarg (gemtuzumab ozogamicin) in patients between 50 and 70 years of age.
        - There was no difference in complete remission rates between the groups.

- The two-year overall survival (OS) rates were 41.9% and 53.2%, respectively; however, after adjustment for factors of prognostic importance (genotype and cytogenetics), there was no difference in OS between groups.

* ***Adults with newly diagnosed AML with Mylotarg (gemtuzumab ozogamicin) as a monotherapy:*** [3]
  - This study compared Mylotarg (gemtuzumab ozogamicin) monotherapy with best supportive care (BSC) in patients who were ineligible for intensive chemotherapy (the median age was 77 years).
  - The median OS was 4.9 months and 3.6 months in the Mylotarg (gemtuzumab ozogamicin) and BSC treatment groups, respectively. This small difference is statistically different but is not likely clinically relevant.
  - Although CD33 status was not part of the inclusion criteria, there was a strong correlation between CD33 expression and OS.

* ***Adults with CD33+ AML in first relapse:*** [4]
  - This single-arm, observational study evaluated remission rates in adults with CD33+ AML who were receiving Mylotarg (gemtuzumab ozogamicin) in their first disease relapse.
  - The rate of complete remission was 26%, with a median relapse-free survival of 11.6 months.
  - The study did not evaluate long-term clinical outcomes and did not compare Mylotarg (gemtuzumab ozogamicin) with any other therapy.

* ***Pediatric patients with relapsed or refractory CD33+ AML:***
  - Approval of Mylotarg (gemtuzumab ozogamicin) in pediatric patients is based on an observational trial in 28 patients with relapsed or refractory CD33+ AML that ranged in age from 2 years to 18 years. Additional case reports from the literature were also included.
  - No differences in efficacy and safety were observed based on age.

- Although induction of remission is a goal of therapy in AML, achieving remission has not been shown to be predictive of long-term benefit such as improved overall survival. None of the current studies establishes a durable clinical benefit with Mylotarg (gemtuzumab ozogamicin) in treating AML. Increased mortality due to hepatic VOD remains a significant risk with this medication.
- Patients with active central nervous system (CNS) leukemia were not included in the pivotal clinical trials, so it is not known if Mylotarg (gemtuzumab ozogamicin) provides any potential benefit in this population.
- The National Comprehensive Cancer Network (NCCN) acute myeloid leukemia (AML) guideline lists Mylotarg (gemtuzumab ozogamicin) as a treatment option for its labeled indications. [5]

Investigational Uses

- There is interest in using Mylotarg (gemtuzumab ozogamicin) in other leukemias, and in high-risk myelodysplastic syndrome (MDS). [6] Studies in these areas are ongoing. There is currently no published evidence in these conditions.
- The NCCN compendium lists Mylotarg (gemtuzumab ozogamicin) as a treatment option for acute promyelocytic leukemia (APL). It also recommends its use in high-risk AML (WBC > 10,000/mcL), regardless of tumor CD33 status, when cardiac issues are present. This use lies outside of package labeling and is not well-supported by clinical evidence. [5]

Safety

- Mylotarg (gemtuzumab ozogamicin) carries a BOX WARNING for hepatotoxicity, including severe or fatal veno-occlusive disease (VOD). [4]
- The overall incidence of hepatic VOD with Mylotarg (gemtuzumab ozogamicin) was approximately 9% based on a safety registry surrounding its prior approval. A pharmacovigilance program identified more than twice the number of hepatic VOD cases as the registry, which puts its overall incidence somewhere between 10% and 20%. [1]
- Hospitalization occurred in 80% of the 99 cases of hepatic VOD that were retrospectively reported in the pharmacovigilance program. Over 66% of these patients died as a result of hepatic VOD. [1]
- A European safety assessment reported an incidence of hepatic VOD of 1% when there was no prior or subsequent hematopoietic stem cell transplant (HSCT) surrounding Mylotarg (gemtuzumab ozogamicin) administration, 19% in patients with a HSCT prior to Mylotarg (gemtuzumab ozogamicin) administration, and 16% when HSCT was received after Mylotarg (gemtuzumab ozogamicin) administration. [1]
- Although dosing of Mylotarg (gemtuzumab ozogamicin) varies from that which was originally approved in 2000, the risk of hepatic VOD remains an active concern as it has also been reported with the newly approved dosing. There are post-marketing requirements in place to attempt to better quantify the risk. [7]

Dosing [4]

Setting	Dose	Schedule	Cycles
Newly diagnosed AML, with daunorubicin and cytarabine (adults)	3 mg/m^2 (up to 4.5 mg)	Days 1, 4, and 7	1 induction cycle
	3 mg/m^2 (up to 4.5 mg)	Day 1 only	2 consolidation cycles
Newly diagnosed AML, with daunorubicin and cytarabine (pediatric patients)	3 mg/m2 (when BSA ≥ 0.6 m^2) 0.1 mg/kg (when BSA < 0.6 m^2)	Once in combination with standard chemotherapy	1 induction cycle
	3 mg/m2 (when BSA ≥ 0.6 m^2) 0.1 mg/kg (when BSA < 0.6 m^2)	Once in combination with standard chemotherapy	1 intensification cycle (no Mylotarg in first or third intensification cycles; during intensification cycle 2 only)
Newly diagnosed AML, as a single agent (adults)	6 mg/m^2 3 mg/m^2	Day 1 Day 8	1 induction cycle
	2 mg/m^2	Day 1, every 4 weeks	Up to 8 (maintenance)
Relapsed/refractory AML, as a single agent (adults or pediatric patients)	3 mg/m^2 (up to 4.5 mg)	Days 1, 4, and 7	Single cycle

Key: AML=acute myeloid leukemia; BSA=body surface area

Cross References
Daurismo, glasdegib, Medication Policy Manual, Policy No. dru585
Idhifa, enasidenib, Medication Policy Manual, Policy No. dru524
Rydapt, midostaurin, Medication Policy Manual, Policy No. dru522
Isocitrate Dehydrogenase-1 (IDH1) Inhibitors (Tibsovo, ivosidenib; Rezlidhia, olutasidenib), Medication Policy Manual, Policy No. dru558
Venclexta, venetoclax, Medication Policy Manual, Policy No. dru462
Vyxeos, daunorubicin liposomal and cytarabine liposomal injection, Medication Policy Manual, Policy No. dru531
Xospata, gilteritinib, Medication Policy Manual, Policy No. dru586

Codes	Number	Description
HCPCS	J9203	Injection, gemtuzumab ozogamicin (Mylotarg), 0.1 mg

References

1. Magwood-Golston JS, Kessler S,Bennett CL. Evaluation of gemtuzumab ozogamycin associated sinusoidal obstructive syndrome: Findings from an academic pharmacovigilance program review and a pharmaceutical sponsored registry. *Leuk Res.* 2016;44:61-4. PMID: 27030962
2. Castaigne S, Pautas C, Terre C, et al. Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study. *Lancet.* 2012;379(9825):1508-16. PMID: 22482940
3. Amadori S, Suciu S, Selleslag D, et al. Gemtuzumab Ozogamicin Versus Best Supportive Care in Older Patients With Newly Diagnosed Acute Myeloid Leukemia Unsuitable for Intensive Chemotherapy: Results of the Randomized Phase III EORTC-GIMEMA AML-19 Trial. *J Clin Oncol.* 2016;34(9):972-9. PMID: 26811524
4. Mylotarg® (gemtuzumab ozogamicin) [package insert]. Wyeth Pharmaceuticals LLC; Philadelphia, PA; August 2021.
5. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology™. [Updated routinely]. [cited with policy updates and as necessary]. Available from: https://www.nccn.org/guidelines/category_1.
6. National Institutes of Health, Clinicaltrials.gov [website]. [cited periodically]. Available from: www.clinicaltrials.gov.
7. Department of Health and Human Services; Food and Drug Administration; BLA 761-060 (Mylotarg, gemtuzumab ozogamicin) Approval Letter. [cited 11/29/2017]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2017/761060Orig1s000Orig2s000ltr.pdf.

Revision History

Revision Date	Revision Summary
9/19/2024	No criteria changes with this annual review.
9/14/2023	The requirement for use of Mylotarg (gemtuzumab ozogamicin) as monotherapy in relapsed/refractory AML was removed for practical reasons (there was no change in clinical evidence).
9/23/2022	There were no changes to coverage criteria with this annual update.
10/15/2021	- Updated COT language. - Clarify the intent of criteria for relapsed/refractory AML, limited to use "as a monotherapy" (no change to policy intent). - Updated quantity limitation and dosing charts with pediatric information
10/28/2020	No changes to coverage criteria with this annual update.
7/22/2020	Updated coverage criteria newly diagnosed AML to include pediatric patients 1 month of age or older, a new FDA approved indication. Added COT language.
10/23/2019	Updated policy with standard language (no change to policy intent).
2/16/2018	New policy.

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Medication Policy Manual | **Policy No:** dru531

Topic: Vyxeos, daunorubicin liposomal and cytarabine liposomal for injection | **Date of Origin:** March 1, 2018

Committee Approval Date: September 19, 2024 | **Next Review Date:** 2025

Effective Date: December 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Vyxeos (daunorubicin liposomal and cytarabine liposomal for injection) is a combination of two chemotherapy drugs in a liposomal formulation. It is an intravenous therapy used in the treatment of some types of acute myeloid leukemia (AML).

PLEASE NOTE: This policy does **not** apply to non-liposomal forms of generic daunorubicin (J9150) or generic cytarabine (J9100 or J9110).

Policy/Criteria

Most contracts require pre-authorization approval of Vyxeos (daunorubicin liposomal and cytarabine liposomal) prior to coverage.

I. Continuation of therapy (COT): Vyxeos (daunorubicin liposomal and cytarabine liposomal) may be considered medically necessary for COT when there is clinical documentation (including, but not limited to chart notes) confirming that criterion A B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Vyxeos (daunorubicin liposomal and cytarabine liposomal) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A and B below are met.

A. A diagnosis of **therapy-related acute myeloid leukemia** (t-AML) or **AML with myelodysplasia-related changes** (AML-MRC) which has not been previously treated (treatment-naïve).

AND

B. Vyxeos (daunorubicin liposomal and cytarabine liposomal) will be used as monotherapy.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Vyxeos (daunorubicin liposomal and cytarabine liposomal) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Vyxeos (daunorubicin liposomal and cytarabine liposomal) will be authorized in quantities up to 9 infusions per lifetime.

IV. Vyxeos (daunorubicin liposomal and cytarabine liposomal) is considered investigational when used for all other conditions, including but not limited to:

A. *De-novo* acute myeloid leukemia.

B. Relapsed or refractory acute myeloid leukemia of any type.

Position Statement

Summary

- Vyxeos (daunorubicin liposomal and cytarabine liposomal) is a combination of two generically available cytotoxic chemotherapeutic drugs in a liposomal formulation. *Note: Pre-authorization is not required for generic daunorubicin or generic cytarabine.*
- Vyxeos (daunorubicin liposomal and cytarabine liposomal) is FDA-approved for the treatment of therapy-related acute myeloid leukemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC) which has not been previously treated (treatment-naïve).
- The intent of this policy is to cover Vyxeos (daunorubicin liposomal and cytarabine liposomal) for the indications and regimen for which it has been shown to be safe and effective, as detailed in the coverage criteria.
- FDA-approval was based on a single pivotal phase 3 trial. This trial has not been published.
- In clinical trials, subjects were treated with up to a total of nine doses as follows: an induction cycle, an optional repeat induction cycle, and up to two consolidation cycles. There is no data to support more than 9 doses per lifetime.
- The safety and effectiveness of Vyxeos (daunorubicin liposomal and cytarabine liposomal) in other conditions has not been established.
- NCCN AML guideline lists Vyxeos (daunorubicin liposomal and cytarabine liposomal) as a category 1 recommendation for initial induction in patients 60 years and over with t-AML and AML-MRC, and as a category 2B recommendation for patients less than 60 years of age. [1]

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy [2]

- Approval was based on a Phase-III, randomized, open-label trial comparing Vyxeos (daunorubicin liposomal and cytarabine liposomal) to standard of care ("7+3" therapy with conventional daunorubicin and cytarabine).
- Vyxeos (daunorubicin liposomal and cytarabine liposomal) was associated with an overall survival (OS) advantage (HR 0.69, 50% CI 0.52-0.9). Median survival was not different between groups (9.56 months, 95% CI 6.6-11.86 vs. 5.95 months, 95% CI 4.99 – 7.75).
- Because the pivotal trial has not been published, study details such as attrition and censoring rules are not available; confidence in these results is correspondingly low.
- The study included subjects from 60-75 years of age; the safety and efficacy of Vyxeos (daunorubicin liposomal and cytarabine liposomal) in younger patients has not been established.

Investigational Uses

- Phase 2 studies in *de-novo* and relapsed/refractory acute myeloid leukemia have not shown any difference in overall survival or 1-year survival. [3,4] Further studies are needed to assess the safety and efficacy of Vyxeos (daunorubicin liposomal and cytarabine liposomal) in these populations.

Cross References
Daurismo, glasdegib, Medication Policy Manual, Policy No. dru585
Idhifa, enasidenib, Medication Policy Manual, Policy No. dru524
Mylotarg, gemtuzumab ozogamicin, Medication Policy Manual, Policy No. dru530
Rydapt, midostaurin, Medication Policy Manual, Policy No. dru522
Isocitrate Dehydrogenase-1 (IDH1) Inhibitors (Tibsovo, ivosidenib, and Rezlidhia, olutasidenib), Medication Policy Manual, Policy No. dru558
Venclexta, venetoclax, Medication Policy Manual, Policy No. dru462
Xospata, gilteritinib, Medication Policy Manual, Policy No. dru586

Codes	Number	Description
HCPCS	J9153	Injection, liposomal, 1 mg daunorubicin and 2.27 mg cytarabine (Vyxeos)

References

1. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology™. [Updated routinely]. [cited with policy updates and as necessary]. Available from: https://www.nccn.org/guidelines/category_1.
2. Vyxeos® (daunorubicin and cytarabine, liposome for injection) [package insert]. Jazz Pharmaceuticals, Inc.; Palo Alto, CA; September 2022.
3. Cortes JE, Goldberg SL, Feldman EJ, et al. Phase II, multicenter, randomized trial of CPX-351 (cytarabine:daunorubicin) liposome injection versus intensive salvage therapy in adults with first relapse AML. *Cancer*. 2015;121(2):234-42. PMID: 25223583
4. Lancet JE, Cortes JE, Hogge DE, et al. Phase 2 trial of CPX-351, a fixed 5:1 molar ratio of cytarabine/daunorubicin, vs cytarabine/daunorubicin in older adults with untreated AML. *Blood*. 2014;123(21):3239-46. PMID: 24687088

Revision History

Revision Date	Revision Summary
9/19/2024	No criteria changes with this annual review.
9/14/2023	No criteria changes with this annual review.
9/23/2022	There were no changes to coverage criteria with this annual update.
10/15/2021	Updated standard COT language (no change to policy intent).
10/28/2020	Updated policy with standard continuation of care (COT) language (no change to policy intent).
10/23/2019	Updated policy with standard language (no change to policy intent).
02/16/2018	New Policy.

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Medication Policy Manual

Policy No: dru535

Topic: Medications for Hereditary Angioedema (HAE)

Date of Origin: July 1, 2018

- Berinert, plasma-derived C1-INH
- Cinryze, plasma-derived C1-INH
- icatibant (generic, Firazyr, Sajazir)
- Kalbitor, ecallantide
- Haegarda, plasma-derived C1-INH
- Orladeyo, berotralstat
- Ruconest, recombinant human C1-INH
- Takhzyro, lanadelumab-flyo

Committee Approval Date: June 20, 2024

Next Review Date: 2024

Effective Date: October 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Medications included in this policy are used to treat hereditary angioedema (HAE). Administration is different for each medication, and may be a subcutaneous injection (SC), intravenous injection (IV), or oral. Kalbitor (ecallantide), icatibant (generic, Firazyr, Sajazir), plasma-derived C esterase inhibitor (pdC1-INH, Berinert), and recombinant human C1-INH (rhC1-INH, Ruconest) are approved for the treatment of HAE attacks. Takhzyro (lanadelumab-flyo) and Orladeyo (berotralstat), are both kallikrein inhibitors, and two other forms of plasma-derived C1-INH (Haegarda and Cinryze), are approved for the prophylaxis of HAE attacks.

Policy/Criteria

Most contracts require pre-authorization approval of medications used to treat hereditary angioedema (HAE) prior to coverage.

I. Continuation of therapy (COT): Medications used to treat HAE may be considered medically necessary for COT when criterion A AND B below are met.

A. One of the following (1, 2, or 3):

1. For diagnoses NOT listed in the coverage criteria below, full policy criteria must be met for coverage.

OR

2. For diagnoses listed in the coverage criteria below, criteria a, b, and c must be met:

a. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

b. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

AND

c. **For use of branded Firazyr or Sajazir:** There is clinical documentation (including, but not limited to chart notes) of an intolerance or contraindication to an inactive ingredient in the generic equivalent medication icatibant.

OR

3. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission. **For use of branded Firazyr or Sajazir:** There is clinical documentation (including, but not limited to chart notes) of an intolerance or contraindication to an inactive ingredient in the generic equivalent medication icatibant.

AND

B. **For Cinryze (plasma-derived C1-INH) ONLY:** Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, Site of Care Review, dru408].

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Medications used to treat HAE may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criterion A, B, or C **AND** D below are met.

A. Hereditary Angioedema (Type I, II, or HAE with normal C1INH (HAE-nl-C1INH)): Acute Treatments (for "as needed" use)

1. Generic icatibant may be considered medically necessary when criteria **a through d below** are met.

2. Berinert (plasma-derived C1-INH), and Kalbitor (ecallantide) may be considered medically necessary when criteria **a through e** are met.

3. Ruconest (recombinant human C1-INH) may be considered medically necessary when criteria **a through f** are met.

4. Brand icatibant (Firazyr, Sajazir) may be considered medically necessary when criteria **a through d and criterion g** are met.

a. A diagnosis of **Type I HAE, Type II HAE, or HAE-nl-C1INH** has been established by, or in consultation with a provider specializing in allergy, immunology, or hematology.

AND

b. Clinical documentation (including, but not limited to chart notes) of serum C4 and C1-INH (antigenic or functional level) that are below the limits of the laboratory's normal reference range (for Type I and Type II HAE only).

AND

c. Clinical documentation (including, but not limited to chart notes) of at least one of the following:

i. Family history of HAE.

OR

ii. Normal level of serum C1q antigenic protein based on the laboratory's normal reference range.

AND

d. The treatment is not used in conjunction with other HAE-specific therapies for acute treatment [e.g., Berinert (plasma-derived C1-INH), Kalbitor (ecallantide), icatibant (generic, Firazyr, Sajazir), or Ruconest (recombinant human C1-INH)].

AND

e. **[Ruconest (recombinant human C1-INH), Berinert (plasma-derived C1-INH) and Kalbitor (ecallantide) only]** Clinical documentation (including, but not limited to chart notes) confirming that generic icatibant has been ineffective, not tolerated, or contraindicated.

AND

f. **[Ruconest (recombinant human C1-INH) only]** Clinical documentation (including, but not limited to chart notes) confirming that treatment with Berinert (plasma-derived C1-INH) has been ineffective, not tolerated, or contraindicated.

AND

g. **[Brand Firazyr or Sajazir only]** There is an intolerance or contraindication to an inactive ingredient in generic icatibant.

OR

B. Hereditary Angioedema (Type I or II): Prophylactic medications (for scheduled use)

1. Haegarda (plasma-derived C1-INH) and Takhzyro (lanadelumab-flyo) may be considered medically necessary when criteria **a through f** are met.

2. Cinryze (plasma-derived C1-INH) and Orladeyo (berotralstat) may be considered medically necessary when criteria **a through g** are met.

a. A diagnosis of **Type I or Type II HAE** has been established by, or in consultation with a provider specializing in allergy, immunology, or hematology.

AND

b. Clinical documentation (including, but not limited to chart notes) of serum C4 and C1-INH (antigenic or functional level) that are below the limits of the laboratory's normal reference range.

AND

c. Clinical documentation (including, but not limited to chart notes) of at least one of the following:

i. Family history of HAE.

OR

ii. Normal level of serum C1q antigenic protein based on the laboratory's normal reference range.

AND

d. The patient has been evaluated for potentially treatable triggers of HAE attacks and is maximally managed with respect to avoiding triggers.

AND

e. A history of attacks that are considered severe with swelling of the face, throat, or gastrointestinal tract. Severe is defined as events that significantly interrupt usual daily activity despite short term symptomatic treatment, as documented in clinical documentation (including, but not limited to chart notes or HAE calendar).

AND

f. The treatment is not used in conjunction with other HAE-specific therapies for the prophylaxis of HAE attacks.

AND

g. **[Cinryze (plasma-derived C1-INH) and Orladeyo (berotralstat) only]** Clinical documentation (including, but not limited to chart notes) confirming that treatment with at least one of the following has been ineffective, not tolerated, or

contraindicated.

i. Haegarda (plasma-derived C1-INH).

OR

ii. Takhzyro (lanadelumab-flyo).

OR

C. Acquired Angioedema: Acute Treatments (for "as needed" use)

1. Generic icatibant may be considered medically necessary in patients with a diagnosis of acquired angioedema when criteria **a through d** are met.

2. Kalbitor (ecallantide) may be considered medically necessary when criteria **a through e** are met.

3. Brand icatibant (Firazyr or Sajazir) may be considered medically necessary when criteria **a through d AND f** are met.

a. A diagnosis of acquired angioedema has been established by, or in consultation with a specialist in allergy, immunology, or hematology.

AND

b. Clinical documentation (including, but not limited to chart notes) of serum C4 and C1-INH (antigenic or functional level) that are below the limits of the laboratory's normal reference range.

AND

c. The patient has been evaluated for an underlying B-cell lymphoproliferative disorder.

AND

d. C1q levels are below the limits of the laboratory's normal reference range.

AND

e. **[Kalbitor (ecallantide) only]** Clinical documentation (including, but not limited to chart notes) confirming that generic icatibant has been ineffective, not tolerated, or contraindicated.

AND

f. **[Brand Firazyr, Sajazir only]** There is an intolerance or contraindication to an inactive ingredient in generic icatibant.

AND

D. For Cinryze (plasma-derived C1-INH) ONLY: Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, Site of Care Review, dru408].

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers icatibant (generic, Firazyr, Sajazir), Takhzyro (lanadelumab-flyo), Orladeyo (berotralstat), and Haegarda (plasma-derived C1-INH) coverable only under the pharmacy benefit (as self-administered medications).

B. Regence Pharmacy Services considers Berinert (plasma-derived C1-INH), Ruconest (recombinant human C1-INH), and Cinryze (plasma-derived C1-INH) coverable under the pharmacy benefit (as self-administered medications) OR coverable under the medical benefit (as provider-administered medications).

C. Regence Pharmacy Services considers Kalbitor (ecallantide) coverable only under the medical benefit (as a provider-administered medication).

D. When pre-authorization is approved, each drug may be covered in the following quantities and for the following authorization periods outlined in Table 1.

Table 1. Quantity and Authorization Limits

Berinert (plasma-derived C1-INH)	Initial: Berinert (plasma-derived C1-INH) may be authorized in a quantity sufficient for the treatment of three attacks per month based on a dose of 20 international units (IU) per kg of body weight per dose. Reauthorization: Authorization shall be reviewed at least every twelve months. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement. Berinert (plasma-derived C1-INH) may be authorized in a quantity sufficient for the treatment of four to six attacks per month, based on a dose of 20 IU per kg of body weight per dose, when criteria 1 below is met: **1.** The patient has been evaluated for potentially treatable triggers of HAE attacks and is maximally managed with respect to avoiding triggers.
Kalbitor (ecallantide)	Initial: Kalbitor (ecallantide) may be authorized in a quantity sufficient for the treatment of three attacks per month (up to nine 10 mg/1 mL vials per month). Reauthorization: Authorization shall be reviewed at least every twelve months. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement. Kalbitor (ecallantide) may be authorized in quantities of ten to eighteen 10 mg/1 mL vials per month (up to six treatments) when criteria 1 below is met: **1.** The patient has been evaluated for potentially treatable triggers of HAE and AAE attacks and is maximally managed with respect to avoiding triggers.
Icatibant (generic, Firazyr, Sajazir)	Initial: Icatibant (generic, Firazyr, Sajazir) may be authorized in a quantity sufficient for the treatment of three attacks per month (up to three 30 mg/3 mL pre-filled syringes per month). Reauthorization: Authorization shall be reviewed at least every twelve months. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement. **For brand**

	icatibant (Firazyr, Sajazir), there must also be documentation of an intolerance or contraindication to an inactive ingredient in generic icatibant. Icatibant (generic, Firazyr, Sajazir) may be authorized in quantities of <u>four to six</u> 30 mg/3 mL pre-filled syringes per month when criteria 1 below is met. **1.** The patient has been evaluated for potentially treatable triggers of HAE attacks and is maximally managed with respect to avoiding triggers.
Ruconest (recombinant human C1-INH)	<u>Initial</u>: Ruconest (recombinant human C1-INH) may be authorized in a quantity sufficient for the treatment of three attacks per month (up to <u>six</u> 2100 IU vials per month). <u>Reauthorization</u>: Authorization shall be reviewed at least every twelve months. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement. Ruconest (recombinant human C1-INH) may be authorized in quantities of up to seven to twelve 2100 IU vials per month (a quantity sufficient for the treatment of 4 to 6 attacks) when criteria 1 below is met: **1.** The patient has been evaluated for potentially treatable triggers of HAE attacks and is maximally managed with respect to avoiding triggers.
Cinryze (plasma-derived C1-INH)	Cinryze (plasma-derived C1-INH) may be authorized in quantities of 1,000 units twice per week for a total of 8,000 units (16 of the 500-unit vials) every 28 days. <u>Reauthorization</u>: Authorization shall be reviewed at least **every twelve months.** Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is effective as defined by at least a 50% decrease in frequency of HAE attacks subsequent to start of therapy, significant improvement/stability in severity and duration of attacks, and clinical documentation of functional improvement/stability.
Haegarda (plasma-derived C1-INH)	Haegarda (plasma-derived C1-INH) may be authorized in quantities up to 60 IU per kg body weight twice weekly. <u>Reauthorization</u>: Authorization shall be reviewed at least **every twelve months.** Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is effective as defined by at least a 50% decrease in frequency of HAE attacks subsequent to start of therapy, significant improvement/stability in severity and duration of attacks, and clinical documentation of functional improvement/stability.

Takhzyro (lanadelumab-flyo)	Initial authorization: Takhzyro (lanadelumab-flyo) may be authorized in quantities up to 300 mg every two weeks, for a total of 600 mg (two of the 300mg/2ml vials) every 28 days for the first twelve months of treatment. Reauthorization: Authorizations shall be reviewed at least **every twelve months.** Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is effective as defined by at least a 50% decrease in frequency of HAE attacks subsequent to start of therapy, significant improvement/stability in severity and duration of attacks, and clinical documentation of functional improvement/stability. Maintenance: After the initial authorization, Takhzyro (lanadelumab-flyo) may be authorized in the following quantities: **a.** Up to 300 mg every four weeks, for a total of 300 mg (one of the 300mg/2ml vials) every 28 days. **OR** **b.** Up to 300 mg every two weeks, for a total of 600 mg (two of the 300mg/2ml vials) every 28 days if clinical documentation is provided that demonstrates the patient has continued to experience HAE attacks, defined as ≥1 attack over the last 6 months, while compliant on stable Takhzyro (lanadelumab-flyo) therapy.
Orladeyo (berotralstat)	Orladeyo (berotralstat) may be authorized in quantities of up to 28 tablets every 28 days. Reauthorization: Authorization shall be reviewed at least **every twelve months.** Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is effective as defined by at least a 50% decrease in frequency of HAE attacks subsequent to start of therapy, significant improvement/stability in severity and duration of attacks, and clinical documentation of functional improvement/stability.

IV. Investigational Uses

A. Combination use of acute treatments for HAE (icatibant [generic, Firazyr, Sajazir], Kalbitor, Ruconest, or Berinert) is considered investigational.

B. Combination use of prophylactic treatments for HAE (Haegarda, Cinryze, Takhzyro, Orladeyo) is considered investigational.

C. Unless other specified, medications included in this policy are considered investigational when used for all other conditions, due to lack of published data, lack of high quality data, or lack of positive data, including for doses in excess of those listed in Section III, Table 1 (above). Details of select investigational uses are listed below in Table 2.

Table 2. Investigational Uses

Acute Medications

Berinert (plasma-derived C1-INH)	1. Treatment of angioedema due to causes other than HAE, including but not limited to drug-induced angioedema, acquired angioedema, allergic angioedema, and idiopathic angioedema. 2. The prophylaxis of HAE attacks.
Kalbitor (ecallantide)	1. Treatment of angioedema due to causes other than HAE or AAE, including but not limited to drug-induced angioedema, allergic angioedema, and idiopathic angioedema. 2. The prophylaxis of HAE or AAE attacks.
Icatibant (generic, Firazyr, Sajazir)	1. Treatment of angioedema due to causes other than HAE, including but not limited to drug-induced angioedema, acquired angioedema, allergic angioedema, and idiopathic angioedema. 2. Angiotensin converting enzyme inhibitor induced angioedema. 3. Prophylaxis of HAE or AAE attacks. 4. Osteoarthritis. 5. Ischemic heart disease.
Ruconest (recombinant human C1-INH)	1. Treatment of angioedema due to causes other than HAE, including but not limited to drug-induced angioedema, acquired angioedema, allergic angioedema, and idiopathic angioedema. 2. The prophylaxis of HAE attacks.

Prophylactic Medications

Cinryze (plasma-derived C1-INH)	1. Angioedema due to causes other than HAE, including but not limited to drug-induced angioedema, acquired angioedema, HAE-nl-C1INH, allergic angioedema, and idiopathic angioedema. 2. Myocardial infarction. 3. Sepsis. 4. Treatment of graft rejection. 5. Prevention of transplant rejection. 6. Stroke.

Haegarda (plasma-derived C1-INH)	1. Angioedema due to causes other than HAE, including but not limited to drug-induced angioedema, acquired angioedema, HAE-nl-C1INH, allergic angioedema, and idiopathic angioedema. 2. Myocardial infarction. 3. Sepsis. 4. Treatment of graft rejection. 5. Prevention of transplant rejection. 6. Stroke.
Takhzyro (lanadelumab-flyo)	1. Angioedema due to causes other than HAE, including but not limited to drug-induced angioedema, acquired angioedema, HAE-nl-C1INH, allergic angioedema, and idiopathic angioedema.
Orladeyo (berotralstat)	1. Angioedema due to causes other than HAE, including but not limited to drug-induced angioedema, acquired angioedema, HAE-nl-C1INH, allergic angioedema, and idiopathic angioedema.

Position Statement

Summary

- HAE is a rare and potentially life-threatening genetic blood disease characterized by inadequate or non-functional C1-INH proteins in the blood. C1-INH protein is a normal component of blood that helps regulate the inflammatory and clotting systems.
- The intent of the policy is to allow for coverage of HAE therapies for the specific diagnoses for which they have been studied when managed by a specialist (as outlined in the coverage criteria), and to limit coverage to doses studied and shown to be safe and effective in clinical trials.
- HAE is diagnosed with clinical presentation, family history and low serum levels of C4 and C1-INH antigenic proteins. HAE with normal levels of C1INH (HAE-nl-C1INH), formerly known as Type III HAE, is suspected in patients with HAE clinical presentation, but levels of C1-INH and C4 are normal, family history is present and serum C1q is also normal. If acquired angioedema (AAE) is suspected due to lack of family history or late onset of symptoms (age over 40 years), C1q antigenic protein testing is used to rule out AAE. Serum C1q level is low in patients with AAE but normal in patients with HAE.[1]
- The symptoms of HAE attacks vary in location and severity. They are highly unpredictable even within the same individual. Symptoms can range from swelling in the extremities or gastrointestinal tract to cases involving the face and throat which are less frequent but could be life threatening.
- Treatment strategies for HAE include long-term prevention, short-term prevention, and on-demand treatment for acute HAE attacks. Medications used in HAE management (other than oral medications) are associated with high healthcare costs.
- Berinert, icatibant (generic, Firazyr, Sajazir), Kalbitor (ecallantide), and Ruconest are FDA-approved for the on-demand treatment of HAE attacks. However, unlike other on-demand treatment options, the effectiveness of Ruconest for the treatment of laryngeal

attacks has not been established. Generic icatibant is the lowest cost of all available options. [2]

- Cinryze, Haegarda, Takhzyro (lanadelumab-flyo), and Orladeyo (berotralstat) are FDA approved for the prophylaxis of HAE attacks. Based on clinical trials, none of the products are superior in terms of safety or efficacy, however, Haegarda and Takhzyro (lanadelumab-flyo) are the lowest costs. Haegarda, lanadelumab, and berotralstat may be self-administered.
- For acute attacks, it is recommended that treatment be initiated as early as possible. Treatment options include Berinert, Kalbitor (ecallantide), icatibant (generic, Firazyr, Sajazir) and Ruconest. There were no preferences given to these acute treatment options.[3]
- Patients with frequent attacks, attacks involving swelling of the face or throat, or incapacitating gastrointestinal attacks may benefit from long-term preventive therapy.
- Patients who are not on long-term preventive therapy that are undergoing surgical or dental procedures may benefit from short-term preventive therapy.
- Strategies in managing HAE should be focused on avoiding or treating triggers, patient's quality of life, and availability of health care resources.
- The World Allergy Organization/European Academy of Allergy and Clinical Immunology (WAO/EAACI), the United States Hereditary Angioedema Associate Medical Advisory Board (US HAEA) and the International/Canadian Hereditary Angioedema guidelines all recommend C1-INH as first line long-term prophylaxis over attenuated androgens, along with the management of potential triggers.[1 4-6].
- HAE-nl-C1INH (formerly known as Type III HAE), is a rare disorder similar to HAE types I and II but is characterized by normal levels of C1-INH, family history and later onset. Treatment options are limited in HAAE-nl-C1INH as no FDA-approved therapies exist and treatment is extrapolated from HAE type I and II treatment.[1]
- Guidelines currently only recommend acute treatment for HAE-nl-C1INH, as evidence for prophylactic treatment is lacking.
- AAE is a rare disorder similar to HAE, as characterized by recurrent episodes of swelling and a deficiency of C1-INH, although AAE develops in older patients and is often associated with lymphoproliferative disorders.[7-9]
- Treatment options for the management of AAE are limited. There are no FDA-approved therapies for AAE and treatment is extrapolated from that of HAE. While no controlled studies have been performed in patients with AAE, observational data from case studies has demonstrated that Kalbitor (ecallantide), icatibant (generic, Firazyr, Sajazir), Berinert (plasma-derived C1-INH), and Ruconest (recombinant human C1-INH) were successfully used to treat AAE attacks. Expert consensus recommendations include these agents for the treatment of AAE. Additionally, management of the underlying lymphoproliferative disorder may control angioedema symptoms.[8-10]
- Given the high cost of medications for the treatment of HAE and AAE, confirmation of efficacy and that current medical necessity criteria are met is required.

Guidelines[1 2 4-6]

- WAO/EAACI and AAAAI guidelines recommend that HAE attacks be treated as early as possible, and that all attacks including those caused by HAE-nl-C1INH and acquired angioedema be considered for on-demand treatment. There is no recommendation on the specific agent used for on-demand therapy.
- WAO/EAACI, US HAEA or the International/Canadian guidelines do not specifically recommend when to initiate prophylaxis as the decision should reflect the disease activity, patient's quality of life, and availability of heath care resources. As such patients should be evaluated for long term prophylaxis once per year.
- In these most recent guidelines, C1-INH medications are recommended as first line therapy for long-term prophylaxis in HAE Types 1 and 2, with attenuated androgens and fibrinolytics recommended as second and third line, respectively.
- Guidelines do not recommend one long term C1-INH prophylaxis agent over the other, therefore Haegarda (plasma derived C1-INH) and Takhzyro (lanadelumab-flyo) are the most cost-effective options. There is insufficient evidence on prophylactic treatment in patients with HAE-nl-C1INH and acquired angioedema, as such use in these patient populations is considered investigational.

Diagnosis[1 2 11 12]

- HAE is diagnosed with clinical presentation, family history, and low serum levels of C4 and C1-INH antigenic proteins (for Type I and Type II only). HAE with normal C1-INH levels (HAE-nl-C1INH)(formerly called Type III) is a subset of rare HAE that largely resembles Type 1 or 2 HAE and may be caused by multiple mutations. However, in many patients with HAE-nl-C1INH, no gene mutation can be found, and the diagnosis is based on family history, normal levels of C4, C-1 INH antigen and function, and normal levels of C1q protein. . Due to normal levels of C1-INH, use of C1INH replacement therapy for long term prophylaxis is controversial, not recommended by guidelines, and evidence of efficacy is anecdotal.
- If acquired angioedema (AAE) is suspected due to lack of family history or late onset of symptoms (age over 40 years), C1q antigenic protein testing is used to rule out AAE. Serum C1q level is low in patients with AAE but normal in patients with HAE.

Clinical Efficacy – Acute Treatments[1 5 8]

- Berinert, Ruconest, icatibant (generic, Firazyr, Sajazir), and Kalbitor (ecallantide) have all demonstrated efficacy in the treatment of acute attacks of HAE. While the body of evidence is generally considered low quality evidence, the products have demonstrated an overall improvement in symptoms following an HAE attack.
- However, the evidence for efficacy of Ruconest contains several notable limitations.
    * Based on a subgroup analysis of the phase 3 trials, there appeared to be decreased efficacy in women and patients located in the United States. While the reason for the difference in treatment effect is unknown, there is uncertainty regarding the clinical effect of Ruconest.
    * Additionally, the effectiveness of Ruconest for the treatment of laryngeal attacks has not been established.

- There are no head-to-head studies comparing treatments for acute HAE attacks.
- The treatment effect of on-demand therapies in HAE-nl-C1INH, (formerly Type III HAE), is uncertain; however, due to the possible influence of bradykinin in some of these patients, Kalbitor (ecallantide) and icatibant (generic, Firazyr, Sajazir) are among the possible treatment options.

Clinical Efficacy – Haegarda[13]

- Approval for Haegarda (pdC1-INH) was based on the COMPACT study, which was a phase 3 randomized, double-blind, placebo-controlled, cross-over study. The study evaluated two doses of Haegarda, but the FDA approved dose is 60 IU/kg.
    * Patients received twice weekly injections of either placebo or weight-based Haegarda (pdC1-INH).
    * Patients included in the study had a history of at least four HAE attacks in the over a 2-month period within 3 months of screening. Attacks must have required immediate treatment, medical attention, or caused significant functional impairment.
    * Patients were permitted to continue oral prophylaxis, but dose changes were not allowed during the study period.
    * Haegarda (pdC1-INH) 60 IU/kg reduced the median number of HAE attacks by 95% compared to placebo. The mean number of attacks per month was 0.52 in the Haegarda (pdC1-INH) period compared to 4.03 during the placebo period. Use of rescue medication was also significantly lower while patients received Haegarda (pdC1-INH).
    * A lower dose of 30 IU/kg was also found to be effective versus placebo but was less effective than the 60 IU/kg dose.
- There are no studies to date evaluating the efficacy of Haegarda (pdC1-INH) compared to other standard treatments for prevention of HAE attacks; however, the COMPACT study included patients who received concomitant attenuated androgens.
- No comparative studies have been performed between attenuated androgens and either Haegarda (pdC1-INH) or Cinryze (pdC1-INH).

Clinical Efficacy – Cinryze[14]

- FDA approval for Cinryze was based on one clinical trial in HAE attack prevention. The study was a prospective, randomized, double-blinded, placebo-controlled multi-center crossover study with 22 HAE patients aged ≥ 6 years of age (range 9 to 73 years) for a 24-week period (12-week placebo and 12-week C1-INH).
    * Patients received twice weekly injections of either placebo or 1,000 units of C1-INH.
    * Patients included in the study had a history of at least two HAE attacks per month. Inclusion was not dependent on the severity of attack.
    * Patients were permitted to continue current medications, but dose changes to androgen or aminocaproic acid were not allowed during the study or 30-days prior to the study.

    * Cinryze (pdC1-INH) reduced the number of HAE attacks by 52% (primary endpoint), the severity of HAE attacks by 32% and duration of swelling by 66% (secondary endpoints). All values were statistically significant.
    * Only half of study patients responded with a 50% or greater reduction in frequency of HAE attacks.
- No comparative studies have been performed between attenuated androgens and Cinryze (pdC1-INH).

Clinical Efficacy – Lanadelumab[15-17]

- FDA approval for lanadelumab was based on one randomized phase 3, double-blind, placebo-controlled trial; the HELP trial. The study evaluated various dosing regimens of lanadelumab. The FDA approved dose of 300 mg every 2 weeks was evaluated for prophylaxis of HAE attacks.
    * Patients included in the study had a history of at least one HAE attacks per 4 weeks.
    * Patients were not permitted to continue current prophylactic medications
    * Treatment with lanadelumab 300 mg subcutaneously every 2 weeks significantly reduced the number of attacks versus placebo (0.257 attacks vs. 1.967, respectively; $p < 0.001$).
    * Treatment with lanadelumab 300 mg subcutaneously every 4 weeks significantly reduced the number of attacks versus placebo (0.526 attacks vs. 1.967, respectively; $p < 0.001$).
    * Treatment with lanadelumab 150 mg subcutaneously every 4 weeks significantly reduced the number of attacks versus placebo (0.480 attacks vs. 1.967, respectively; $p < 0.001$).
    * Additionally, the lanadelumab group had less rescue medication use and a lower number of moderate to severe HAE attacks compared to the placebo-group.
- In patients with no HAE attacks in the past 6-months while on lanadelumab, a dose reduction to 300mg every 4 weeks has been shown to be safe and effective.
- No comparative studies have been performed between attenuated androgens, C1-INH, and lanadelumab.
- Doses higher than 300 mg every 2 weeks were not studied during clinical trials.
- There are no trials of Takhzyro (lanadelumab) used in combination with Haegarda (C1-INH) or any other HAE prophylactic agent; therefore, use of Takhzyro (lanadelumab) in combination with any other HAE prophylactic agent is considered investigational.

Clinical Efficacy – Berotralstat[18]

- FDA approval for berotralstat was based a single phase 3, multicenter, randomized, double-blind, placebo-controlled trial; the APEX-2 trial. The study evaluated two doses of berotralstat.
    * Patients included in the study had a history of at least one HAE attacks per 4 weeks (≥2 investigator confirmed HAE attacks in the 56-day run-in period).

    * Patients were not permitted to continue current prophylactic medications
    * Treatment with berotralstat 110 mg by mouth every day significantly reduced the monthly rate of attacks versus placebo (1.65 attacks vs. 2.35, respectively; p = 0.024).
    * Treatment with berotralstat 150 mg by mouth every day significantly reduced the monthly rate of attacks versus placebo (1.31 attacks vs. 2.35, respectively; p < 0.001).
    * Additionally, the berotralstat groups had less rescue medication use compared to the placebo-group.
- No comparative studies have been performed between attenuated androgens, C1-INH, lanadelumab and berotralstat.
- Doses higher than 150 mg every day were not studied during clinical trials.

Investigational Uses

- C1-INH is currently being studied in a variety of other conditions including angioedema due to causes other than HAE, myocardial infarction, and sepsis; however, due to lack of published data, it is considered investigational in these conditions.
- Icatibant (generic, Firazyr, Sajazir) is currently being studied in a variety of other conditions including angioedema due to causes other than HAE, prevention of HAE attacks, osteoarthritis, and ischemic heart disease; however, due to lack of published data, it is considered investigational in these conditions.

Safety

- The most common adverse reactions with Berinert are injection site nausea, headache, dysgeusia, abdominal pain, and vomiting. Other rare but serious adverse events include hypersensitivity and thromboembolic events. There is also a risk for the transmission of infectious agents (e.g. viruses) because Berinert is derived from human blood.[19]
- The most common adverse reactions with Ruconest are headache, nausea, and diarrhea. Other rare but serious adverse events include hypersensitivity and thromboembolic events.[20]
- The most common adverse reactions with icatibant (generic, Firazyr, Sajazir) are injection site reactions (97%), such as erythema (redness of skin) and swelling. Other common adverse reactions (> 1%) included pyrexia, increased liver enzymes, dizziness, and rash.[21 22]
- Kalbitor (ecallantide) is given subcutaneously and carries a boxed warning for anaphylactic reactions (3.9%). Due to the risk of anaphylaxis Kalbitor (ecallantide) should only be administered by a healthcare professional with appropriate medical support to manage anaphylaxis and hereditary angioedema.[23]
- The most common adverse reactions with Kalbitor (ecallantide) are headache, nausea, diarrhea, pyrexia, injection site reactions, and nasopharyngitis.[23]
- The most common adverse events reported with plasma-derived Haegarda include injection site reactions, hypersensitivity, nasopharyngitis, and dizziness. Of the injections site reactions reported in clinical trials, 95% were of mild intensity and 83% resolved within one day of onset.[24]

- The most common side effects experienced during lanadelumab clinical trials included injection site reactions, rash, dizziness, upper respiratory infections, headache, diarrhea and myalgia.[17]
- The most common side effects experienced during berotralstat clinical trials included upper respiratory tract infection, abdominal pain, diarrhea, headache, and back pain.[25]
- Plasma-derived C1-INH replacement therapy has a long history of use without evidence of drug interactions or immunogenicity. No cases of pathogen transmission have been reported.[2]

Appendix 1: Oral Prophylactic Medications for Hereditary Angioedema[3 26 27]

Drug	Usual Adult Dose	Dosage Range	FDA Approved for HAE
danazol (Danocrine)	200 mg/day	100 mg every 3 days – 600 mg/day	Yes
stanozolol (Winstrol)	2 mg/day	1 mg every 3 days – 6 mg/day	Yes
oxandrolone (Oxandrin)	10 mg/day	2.5 mg every 3 days – 20 mg/day	No
epsilon aminocaproic acid (Amicar)	2 g three times/day	1 g twice/day – 4 g three times/day	No
tranexamic acid (Lysteda)	20-50 mg/kg/day	3-6 g/day maximum	No

Appendix 2: FDA-Approved, HAE-specific Medications			
Drug	**Indication**	**Usual Dose and Route**	**Approved for Self-Administration**
Kalbitor (ecallantide)[23]	Treatment of acute attacks of HAE	30 mg injected subcutaneously in three 10 mg injections	No
icatibant (generic, Firazyr, Sajazir)[21 22]	Treatment of acute attacks of HAE	30 mg injected subcutaneously to the abdominal area	Yes
Berinert (pdC1-INH)[19]	Treatment of acute attacks of HAE	20 IU per kg injected intravenously	Yes
Ruconest (rhC1-INH)[20]	Treatment of acute attacks of HAE Limitation of Use: Effectiveness was not established in HAE patients with laryngeal attacks	50 IU per kg injected intravenously; Max dose 4200 IU	Yes
Cinryze (IV plasma derived C1-INH)[14]	Routine prophylaxis to prevent HAE attacks	1000 U IV twice weekly (every 3 to 4 days)	Yes
Haegarda (SC plasma-derived C1-INH) [24]	Routine prophylaxis to prevent HAE attacks	60 IU/kg SC twice weekly (every 3 to 4 days)	Yes
Takhzyro (lanadelumab-flyo)[17]	Routine prophylaxis to prevent HAE attacks	300mg SC every two weeks	Yes
Orladeyo (berotralstat) [25]	Routine prophylaxis to prevent HAE attacks	150mg PO daily	Yes

Codes	Number	Description
HCPCS	J1290	Injection, ecallantide (Kalbitor), 1 mg
HCPCS	J0597	Injection, c-1 esterase inhibitor (human), Berinert, 10 units
HCPCS	J0598	Injection, c-1 esterase inhibitor (human), Cinryze, 10 units
HCPCS	J0596	Injection, c1 esterase inhibitor (recombinant), Ruconest, 10 unit

Cross References
Site of Care Review, Medication Policy Manual, Policy No. dru408

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Revision History

Revision Date	Revision Summary
6/20/2024	Added Cinryze (plasma-derived C1-INH) to site of care (SOC) program (effective 10/1/2024).
12/7/2023	• Updated reauthorization time frame to 12 months for all HAE medications in this policy.
12/9/2022	• Added Sajazir (icatibant), newly approved medication, to the policy. • Added step therapy requirement with Berinert (plasma-derived C1-INH) to Ruconest (recombinant human C1-INH) for acute HAE treatment. • Removed step through attenuated androgens/antifibrinolytics for prophylactic HAE treatments. • Clarified HAE-nl-C1INH (formerly Type III HAE) diagnosis and treatment, with prophylactic treatment considered investigational.
1/20/2021	• Added Orladeyo (berotralstat), a newly-approved medication, to the policy. • Added generic icatibant step therapy requirement for all acute HAE therapies. • Removed Haegarda step therapy requirement for Takhzyro (lanadelumab-flyo). • Clarified reauthorization criteria and quantity limits for maintenance Takhzyro (lanadelumab-flyo) therapy.
1/22/2020	• Added step therapy requirement with generic icatibant to brand Firazyr (icatibant). • Added continuation of therapy (COT) criteria (no change to intent of coverage criteria).
1/31/2019	No criteria changes with this annual update.
11/16/18	Added Takhzyro (lanadelumab-flyo), a newly-approved medication, to the policy (effective January 1, 2019).
2/19/2018	• New policy (effective July 1, 2018): All existing HAE policies have been combined into a single policy, with no overall change to the intent of coverage criteria. • Added a criterion clarifying that multiple treatments for acute attacks of HAE should not be used concurrently. • Extended the authorization period to 6 months from 3 months for all medications.

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Medication Policy Manual **Policy No:** dru538

Topic: Monoclonal antibodies for asthma and other immune conditions

- Cinqair, reslizumab
- Fasenra, benralizumab
- Nucala, mepolizumab
- Tezspire, tezepelumab-ekko
- Xolair, omalizumab

Date of Origin: April 1, 2018

Committee Approval Date: June 20, 2024 **Next Review Date:** 2025

Effective Date: September 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Medications included in this policy are monoclonal antibodies that target specific proteins to treat several immune diseases such as severe asthma and chronic idiopathic urticaria. Administration is via subcutaneous (SC) or intravenous (IV) injection.

Policy/Criteria

Most contracts require pre-authorization approval of monoclonal antibodies for asthma and other immune conditions prior to coverage.

I. Continuation of therapy (COT): Monoclonal antibodies for asthma and other immune conditions may be considered medically necessary for COT when criteria A **AND** B below are met.

A. One of the following (1, 2, or 3):

1. For diagnoses NOT listed in the coverage criteria below, criteria a and b must be met:

a. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

b. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

2. For diagnoses listed in the coverage criteria below, criteria a and b must be met:

a. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

b. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

3. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

AND

B. For provider-administered medications: site of care administration requirements are met [refer to Medication Policy Manual, Site of Care Review, dru408].

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve) patients: Monoclonal antibodies for asthma and other immune conditions may be considered medically necessary when criteria A and B below are met.

A. One of the following diagnostic criteria 1 through 6 below are met.

1. Asthma:

Fasenra (benralizumab), Nucala (mepolizumab), Cinqair (reslizumab), or Xolair (omalizumab), or Tezspire (tezepelumab-ekko) may be considered medically necessary for severe asthma when there is clinical documentation (including, but not limited to chart notes) that criteria a through e below are met.

a. Patient is currently followed by an asthma specialist (allergist, immunologist, or pulmonologist).

AND

b. Adherent use of maximally tolerated inhaled corticosteroids (ICS) and long-acting inhaled beta-2 agonist (LABA) therapy (see *Appendices 1 and 2*) has been ineffective as defined by at least one of the following markers of uncontrolled asthma within the previous 12 months (as defined in criterion i, ii, or iii below):

i. Treatment with a course of oral corticosteroids (e.g., steroid bursts).

OR

ii. An emergency department (ED) visit or hospitalization.

OR

iii. There is clinical documentation of poor asthma control as demonstrated by limitation of activities of daily living (ADLs), nighttime awakening, or dyspnea.

AND

c. An evaluation has been performed to assess for underlying conditions or triggers for asthma or pulmonary disease. If identified, a documented plan is in place to address these.

AND

d. ***[*For *Fasenra (benralizumab), Nucala (mepolizumab), and Cinqair (reslizumab) only]*:** A blood eosinophil count of at least 150 cells/µL in the past 12 months.

AND

e. ***[For Xolair (omalizumab) only]*:** A diagnosis of **severe extrinsic (allergic) asthma** and criteria i and ii below are met:

i. Positive skin prick test or in-vitro specific IgE test (such as RAST, MAST, FAST, ELISA) to one or more allergens, (or is currently receiving specific immunotherapy like allergy shots) which support the patient's clinical history.

AND

ii. Total serum IgE level is one of the following (1 or 2 below):

1) For patients ≥12 years of age: 30 to 700 IU/ml

OR

2) For patients age 6 to <12 years of age, based on weight, as follows in a) to g) below:

a) >90 to 150 kg: 30 to 300 IU/ml.

b) >70 to 90 kg: 30 to 500 IU/ml.

c) >60 to 70 kg: 30 to 600 IU/ml.

d) >50 to 60 kg: 30 to 700 IU/ml.

e) >40 to 50 kg: 30 to 900 IU/ml.

f) >30 to 40 kg: 30 to 1,100 IU/ml.

g) 20 to 30 kg: 30 to 1,300 IU/ml.

OR

2. Chronic idiopathic/Spontaneous Urticaria (CIU/CSU):

Xolair (omalizumab) may be considered medically necessary for CIU/CSU when there is clinical documentation (including, but not limited to chart notes) that all criteria a through e below are met.

a. Specialist evaluation: Patient has been evaluated by and is currently followed by a specialist (allergist, immunologist, pulmonologist, dermatologist).

AND

b. A diagnosis of chronic idiopathic/spontaneous urticaria and current urticarial flares as supported by i and ii below:

i. Documentation of spontaneous flares: Spontaneous urticarial flares, despite avoidance of triggers (in the absence of potential triggers).

PLEASE NOTE: Urticarial flares may also occur in the presence of a trigger ("inducible urticaria"). However, patients may have a mixed diagnosis of CSU/CIU, along with inducible urticaria. The intent of this criterion is for documentation of spontaneous flares, in the absence of a trigger.

AND

ii. Comprehensive evaluation: An evaluation has been performed to rule out other causes of urticaria and identify potential triggers, and a trigger management plan is in place, if applicable.

AND

c. Trigger avoidance: Underlying conditions or identified triggers for urticaria are being maximally managed, including a trigger avoidance management plan for any identified triggers to reduce flares.

AND

d. Documented functional impairment due to poor urticaria control or exacerbations, which may include (but is not limited to) documentation of limitation of activities of daily living (ADLs), such as missing school or work or insomnia due to itching.

AND

e. Maximal antihistamine step therapy: The patient is compliant with H1 antihistamines (see *Appendix 3*) at the maximally tolerated doses consistent with current guidelines, unless contraindicated.

PLEASE NOTE: Clinical documentation of initial urticaria workup, as well as subsequent visits, should be submitted for review.

OR

3. Eosinophilic Granulomatosis with Polyangiitis (EGPA, formerly known as Churg-Strauss Syndrome):

Nucala (mepolizumab) may be considered medically necessary for EGPA when there is clinical documentation (including, but not limited to chart notes) that criteria a, b, and c below are met.

a. A specialist (allergist, immunologist, pulmonologist, or rheumatologist) has established the diagnosis and is currently following the patient.

AND

b. The patient has a diagnosis of EGPA confirmed by either criterion i or ii below:

i. The patient meets **at least four** of the six criteria (1 to 6) below:

1) History of asthma (wheezing or the finding of diffusion high-pitched wheezes in expiration).

2) Blood eosinophil count of greater than 10% (% EOS) on differential white blood count (diff WBC).

3) Peripheral neuropathy.

4) Migratory or transient pulmonary opacities detected radiographically (such as on chest X-ray; CXR).

5) Paranasal sinus abnormality.

6) Blood vessel biopsy (such as artery, arteriole, or venule) with extravascular eosinophils.

OR

ii. The patient meets ALL of the following criteria 1, 2, and 3 below:

1) Medical history of asthma.

AND

2) Peak blood eosinophil count of greater than 1500 cells/microliter.

AND

3) Systematic vasculitis involving two or more extra-pulmonary organs.

AND

c. The patient has a history of EGPA for at least 6 months with a history of relapsing or refractory disease and criteria i and ii below are met.

i. Currently on maximally tolerated oral corticosteroid within the past 90 days, unless not tolerated or contraindicated.

AND

ii. Treatment with an oral DMARD (such as azathioprine or methotrexate) in the past 90 days has been ineffective, not tolerated, or all oral DMARDs are contraindicated.

OR

4. Hypereosinophilic Syndrome (HES):

Nucala (mepolizumab) may be considered medically necessary for HES when there is clinical documentation (including, but not limited to chart notes) that criteria a, b, and c below are met.

a. A specialist (allergist, dermatologist, immunologist, hematologist, neurologist, or pulmonologist) has established the diagnosis and is currently following the patient.

AND

b. The patient has a diagnosis of HES and criteria i and ii below are met.

i. FIP1L1-PDGFRA–negative.

AND

ii. Peak blood eosinophil count of greater than 1000 cells/microliter.

AND

c. The patient has a history of flares and criteria i and ii below are met.

i. Treatment with an adequate course (at least four weeks) of oral corticosteroids within the past 6 months, unless not tolerated or contraindicated.

AND

ii. Persistent HES symptoms despite adequate treatment (at least four weeks) with a steroid-sparing therapy (as listed in Appendix 4) within the past 6 months has been ineffective, not tolerated, or all are contraindicated.

OR

5. Nasal Polyps:

Xolair (omalizumab) or Nucala (mepolizumab) may be considered medically necessary for nasal polyps when there is clinical documentation (including, but not limited to chart notes) that criteria a through f below are met.

a. The diagnosis has been established by a specialist in allergy, immunology, or otolaryngology.

AND

b. Documented recurrent, persistent, and/or current symptomatic nasal polyps, defined as meeting one of the following (i or ii) below:

i. The nasal polyps are currently documented as bilateral.

OR

ii. A history of recurrent bilateral nasal polyps, requiring more than one nasal polypectomy.

AND

c. Persistent symptomatic nasal polyps despite maximal medical treatment with both of the following (i and ii), unless ineffective, contraindicated, or not tolerated:

i. A corticosteroid used intranasally (INCS) for at least 12 weeks, as documented by detailed chart notes, including but not limited to a non-prescription INCS, INCS eluding stent) or pharmacy claims (for prescriptions INCS).

AND

ii. At least one 5-to-14-day course of oral corticosteroids in the past two years.

AND

d. There is a treatment plan for use in combination with an intranasal corticosteroid.

AND

e. Documented functional impairment due to CRSwNP, including but not limited to poor sleep quality, loss of smell, symptomatic nasal obstruction, and/or facial pain.

AND

f. **For Xolair (omalizumab) only:** Total serum IgE level is between 30 IU/ml and 1500 IU/ml.

OR

6. IgE-mediated food allergy:

Xolair (omalizumab) may be considered medically necessary for IgE-mediated food allergy when there is clinical documentation (including, but not limited to chart notes) that criteria a. through e. below are met:

a. Multiple confirmed allergies: A diagnosis of an IgE-mediated food allergy to peanut **and** *at least* one other food allergy, confirmed by a positive result of at least one of the following (i., ii, and/or iii):

i. A skin prick test (SPT) to the offending food allergens.

OR

ii. A food-specific IgE test to the specific offending food allergens.

OR

iii. A oral food challenge to the offending food allergens.

AND

b. Age: The patient is 1-17 years old at the start of Xolair (omalizumab) therapy.

AND

c. Specialist: Xolair (omalizumab) is prescribed by an allergist or immunologist.

AND

d. Severity: Documentation of at least one significant allergic reaction to all of the offending food allergens, defined as meeting all of the following criteria (i., ii., and iii.):

i. The reaction was a significant *systemic* allergic reaction with documented symptoms including, but not limited to, hives, swelling, wheezing, hypotension, gastrointestinal symptoms, and/or anaphylaxis.

AND

ii. The reaction occurred within a short time frame (up to 2 hours) following ingestion of the offending food allergen.

AND

iii. The reaction prompted a medical intervention (including, but not limited to, the use of an epinephrine rescue device, a visit to the emergency department or urgent care, or hospitalization).

AND

e. Ongoing avoidance: There is a treatment plan for use in conjunction with ongoing food allergen avoidance.

AND

B. **For provider-administered medications** (per *Table 1*): Site of care administration requirements are met [refer to Medication Policy Manual, Site of Care Review, dru408].

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers products in this policy covered per the administration and benefits as detailed in *Table 1*:

Table 1. Provider- versus Self-administered Products

Provider-Administered Product Pharmacy Services considers the following under the medical benefit (as provider-administered medications):	**Coverable Self-Administered Alternatives** Pharmacy Services considers the following coverable under the pharmacy benefit (as self-administered medications):
- Fasenra (benralizumab) PFS	- Fasenra (benralizumab) autoinjector
- Nucala (mepolizumab) vials - Nucala (mepolizumab) PFS [a]	- Nucala (mepolizumab) autoinjector - Nucala (mepolizumab) PFS [a]
- Xolair (omalizumab) vials - Xolair (omalizumab) PFS [a]	- Xolair (omalizumab) PFS [a] - Xolair (omalizumab) autoinjector
- Cinqair (reslizumab) vials	- Fasenra (benralizumab) autoinjector - Nucala (mepolizumab) autoinjector - Nucala (mepolizumab) PFS[a]
- Tezspire (tezepelumab-ekko) vials - Tezspire (tezepelumab-ekko) PFS	- Tezspire (tezepelumab-ekko) single-use autoinjector

[a] Pharmacy Services considers this product coverable under the pharmacy benefit (as a self-administered medication) **OR** coverable under the medical benefit (as a provider-administered medication).
PFS = pre-filled syringe

B. When pre-authorization is approved, each drug will be covered in the following quantities and for the following authorization periods outlined in *Table 2*.

TABLE 2. Authorization Limits

Product	**Authorization Limits**
Cinqair (reslizumab)	**Severe eosinophilic asthma:** - Up to 3 mg/kg every 28 days. - Authorization **may** be reviewed at least every 12 months to confirm that current medical necessity criteria are met and the medication is effective, defined as sustained clinical improvement from reduced asthma symptoms (such as reduced missed days from work or school) or stable asthma control.
Fasenra (benralizumab)	**Severe eosinophilic asthma:** 12 years of age and older: Up to 8 doses (30mg/ml PFS or 30mg/ml autoinjector; dosage form per *Table 1*) in a 52-week period, based on recommended initial dosing of 30 mg every 4 weeks for 3 doses, followed by 30 mg every 8 weeks. 6 years to 11 years of age: - Weighing less than 35 kg: Up to 8 doses (10mg/ml PFS) in a 52-week period, based on recommended initial dosing of 10mg every 4 weeks for 3 doses, followed by 10mg every 8 weeks.

Product	Authorization Limits
	- Weighing 35 kg or more: Up to 8 doses (30mg/ml PFS or 30mg/ml autoinjector; dosage form per *Table 1*) in a 52-week period, based on recommended initial dosing of 30mg every 4 weeks for 3 doses, followed by 30mg every 8 weeks. Authorization **may** be reviewed at least every 12 months to confirm that current medical necessity criteria are met and the medication is effective, defined as sustained clinical improvement from reduced asthma symptoms (such as reduced missed days from work or school) or stable asthma control.
Nucala (mepolizumab)	**Severe eosinophilic asthma:** - Up to 100 mg (one vial, PFS, or autoinjector; dosage form per *Table 1*) every 28 days. - Authorization **may** be reviewed at least every 12 months to confirm that current medical necessity criteria are met and the medication is effective, defined as sustained clinical improvement from reduced asthma symptoms (such as reduced missed days from work or school) or stable asthma control. **Eosinophilic Granulomatosis with Polyangiitis (EGPA) or Hypereosinophilic Syndrome (HES):** - Up to 300 mg (three – 100 mg vials, three – 100 mg PFS, or three – 100 mg autoinjectors; dosage form per *Table 1*) every 28 days for up to 12 months. - Authorization **shall** be reviewed at least every 12 months to confirm that current medical necessity criteria are met and the medication is effective, defined as disease stability, improvement, or decreased corticosteroid dose. **Nasal Polyps:** - Up to 100mg (one vial, PFS, or autoinjector every 28 days. - Reauthorization: Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, that there is ongoing INCS use, and that the medication is effective, defined as sustained clinical improvement from reduced symptoms from nasal polyps (such as improved sleep quality, sense of smell, reduction in nasal obstruction symptoms, and/or facial pain) or stable CRSwNP control. - Authorization **may** be reviewed at least every 12 months.
Tezspire (tezepelumab-ekko)	**Severe asthma:** - 210 mg (one vial, pre-filled syringe, or pen) every 28 days. - Authorization **may** be reviewed at least every 12 months to confirm that current medical necessity criteria are met and the medication is effective, defined as sustained clinical improvement from reduced asthma symptoms (such as reduced missed days from work or school) or stable asthma control.
Xolair (omalizumab)	**Severe extrinsic (allergic) asthma:** - Up to 375 mg every 14 days [375 mg dose supplied as up to three - single-dose 150 mg vials (total of 3 mL) OR two - 150 mg and one - 75 mg PFS or autoinjector (total of 2.5 mL) OR one - 300mg and one - 75mg PFS or autoinjector (total of 2.5 ml); dosage form per *Table 1*]. - Authorization **may** be reviewed at least every 12 months to confirm that current medical necessity criteria are met, and the medication is effective defined as sustained clinical improvement from reduced asthma/ symptoms (such as reduced missed days from work or school) or stable asthma control.

Product	Authorization Limits
	Chronic Idiopathic/ Spontaneous urticaria (CIU/CSU): - Initial Authorization: Up to 300 mg every 28 days [300 mg dose supplied as up to two - 150 mg single-dose vials OR two - 150 mg PFS or autoinjectors (total of 2 ml) OR one - 300mg PFS or autoinjector (total of 2 ml); dosage form per *Table 1*]. - Reauthorization: o Authorization **may** be reviewed at least every 12 months to confirm that current medical necessity criteria are met and the medication is effective defined as sustained clinical improvement from reduced urticaria symptoms (such as reduced missed days from work or school) or stable asthma control. o Doses of up to 600 mg every 28 days (such as 300 mg every 14 days) may be authorized on a case-by-case basis if documentation of objective measures supporting the need for more frequent dosing are provided, including documentation of partial response to starting dosing but incomplete urticaria control. **Nasal Polyps:** - Up to 600 mg every 14 days [600 mg dose supplied as up to four – single-dose 150 mg vials, PFS or autoinjectors (total of 4 mL) OR up to two – 300 mg PFS or autoinjectors (total of 4 ml); dosage form per *Table 1*]. - Reauthorization: Authorization **may** be reviewed at least every 12 months. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, that there is ongoing INCS use and that the medication is effective defined as sustained clinical improvement from reduced symptoms from nasal polyps (such as improved sleep quality or sense of smell, reduction in nasal obstruction symptoms and/or facial pain) or stable CRSwNP control. **IgE-Mediated Food Allergy:** - Initial authorization (6 months): up to 600mg every 14 days [600 mg dose supplied as up to two 300 mg PFS or autoinjectors (total of 4 ml) OR up to four 150 mg single-dose vials, PFS or autoinjectors (total of 4 ml); dosage form per *Table 1*]. - Reauthorization Authorization **SHALL** be reviewed at least every 12 months. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and BOTH of the following (1. and 2.): 1. That there is ongoing food allergen avoidance. 2. That the medication is effective, defined as a reduction in severe food allergens reactions requiring medical care. *This may include reduction the frequency and/or severity of allergic reactions to the offending food(s), AND a reduction in the need for additional medical care, such as rescue epinephrine (EpiPen) use, urgent care or emergency department visits, or hospitalizations.*

IV. Not Medically Necessary Uses

A. Respiratory monoclonal antibodies [as listed in *Table 1*, including, but not limited to, Xolair (omalizumab)] are considered not medically necessary when used for allergic rhinitis.

V. Investigational Uses

A. Combination use of any anti-IL-5, anti-IgE, anti TSLP, or anti IL-4 monoclonal antibodies in this and other policies (see *Cross References).*

B. Dose escalations (such as for partial or non-response) in excess of those listed in the "Quantity Limitations," *Table 2* (above) is considered investigational for any indication.

C. Unless otherwise specified in the coverage criteria above, medications included in this policy are considered investigational when used for all other conditions, due to lack of published data, lack of high-quality data, or lack of positive data. Details of select investigational uses are listed (in *Table 3*) below.

Table 3. Investigational Uses

Allergic bronchopulmonary aspergillosis (ABPA)	- There is insufficient evidence to establish the efficacy of monoclonal anti-IgE or anti-IL-5 antibodies for the treatment of ABPA. - The one small crossover trial (n=13) found a reduction in exacerbations over a 4-month period in ABPA patients with use of high-dose Xolair (omalizumab) (750 mg monthly) (p=0.048); however, the long-term clinical benefit is unknown. Additional research is needed to clarify the safety, efficacy, and optimal dosing of Xolair (omalizumab) for ABPA. [1]
Atopic dermatitis (AD)	- There is insufficient evidence to support the use of monoclonal anti-IgE or anti-IL-5 antibodies for atopic dermatitis. [2 3] - Nucala (mepolizumab) has been studied in atopic dermatitis, and no significant benefit was observed.
Chronic eosinophilic pneumonia (CEP)	- There is insufficient published evidence for the use of monoclonal anti-IgE or anti-IL-5 antibodies for the treatment of CEP. - In addition, no ongoing trials were identified for monoclonal anti-IgE or anti-IL-5 antibodies for the treatment of CEP. [4]
Chronic obstructive pulmonary disease (COPD)	- There is no reliable evidence to establish efficacy or safety of monoclonal anti-IgE, anti-IL-5, or anti-TSLP antibodies for the treatment of eosinophilic COPD. - Nucala (mepolizumab) was studied in two phase 3 trials evaluating annual COPD exacerbation rate; however, the benefit with Nucala (mepolizumab) was not consistently demonstrated in patients with eosinophilic COPD. Despite promising results of clinical trials, high-quality, long-term clinical trials are needed to confirm efficacy and safety of Nucala (mepolizumab) in this setting. [5] - Additional studies are ongoing for Fasenra (benralizumab) and Tezspire (tezepelumab-ekko). [4]

Table 3. Investigational Uses	
Eosinophilic esophagitis (EE)	- There is no reliable evidence to establish efficacy or safety of monoclonal anti-IgE or anti-IL-5 antibodies in the treatment of eosinophilic esophagitis. - One small trial found no benefit of Xolair (omalizumab) in patients with eosinophilic esophagitis. [6]
Eosinophilic granulomatosis with polyangiitis (EGPA) / allergic granulomatosis / Churg-Strauss syndrome	- Except as noted in the coverage criteria, the use of monoclonal anti-IgE or anti-IL-5 antibodies in the treatment of EGPA is investigational. - There are no published clinical trials evaluating the safety or efficacy of Xolair (omalizumab), Fasenra (benralizumab), and Cinqair (reslizumab) for the treatment of EGPA. Additional studies are ongoing for Fasenra (benralizumab) and Cinqair (reslizumab). [7]
Hypereosinophilic syndrome (hyper E, HES)	- Except as noted in the coverage criteria, the use of monoclonal anti-IgE or anti-IL-5 antibodies in the treatment of HES is investigational. - One small phase 2 of Fasenra (benralizumab) in patients with symptomatic PDGFRA-negative HES reported a superior rate of reduction in eosinophil count at week 12 as compared to placebo. [8] A phase 3 trial is ongoing to evaluate clinical outcomes (HES flares). [4]
IgE-mediated food allergies (other than noted in the coverage criteria above)	- *In adults*: There is insufficient evidence to establish the safety and efficacy of Xolair (omalizumab) used in adults (age ≥ 18 years old) for the treatment of food allergies. - *Testing*: Use of Xolair (omalizumab) for treatment of food allergy determined by tests (other than listed in the coverage criteria) is considered investigational and not coverable. - *Other food allergies (not listed in the coverage criteria):* There is insufficient evidence to establish the efficacy of monoclonal anti-IgE and anti-IL-5 antibodies for the treatment of food allergies (other than specifically listed in the criteria above) including for the use of Xolair (omalizumab) in patients without a documented peanut allergy OR for an isolated peanut allergy.

Position Statement

Summary

Monoclonal anti-IgE and anti-IL-5, and anti-TSLP antibodies may be covered for specific diagnoses where there is demonstrated safety and efficacy from randomized, controlled trials to support their use, including asthma and other specific indications.

- Anti-IgE monoclonal antibodies [e.g., Xolair (omalizumab)] reduces the levels of circulating immunoglobulin E (IgE) and inhibits binding of IgE to mast cells, to prevent the activation of the allergic cascade and decrease inflammation.
- Anti-IL-5 antibodies [e.g., Fasenra (benralizumab), Nucala (mepolizumab), and Cinqair (reslizumab)] prevent activation of interleukin 5 (IL-5) that is responsible for the growth and survival of eosinophils, to decrease inflammation.

- Anti-TSLP antibodies [e.g., Tezspire (tezepelumab-ekko)] prevent activation of the TSLP cytokine that is responsible for modulating the downstream pathway involved in the epithelial cell inflammatory response. [10]
- Interleukin-4 receptor antagonist [IL-4; Dupixent (dupilumab)] is also used for add-on maintenance treatment for asthma (covered in a separate policy; see *Cross References*).

Asthma

- Monoclonal respiratory antibodies may be coverable for poorly controlled asthma despite use of maximal step therapy, which includes patient compliance with therapy, an assessment for triggers, and a plan to control identified triggers.
- Monoclonal respiratory antibodies may be covered when there is documentation of uncontrolled severe asthma with utilization of other appropriate medications, as detailed in the coverage criteria. Use of monoclonal respiratory antibodies for management outside of these criteria are not coverable.
- For severe asthma (STEP 5), Global Initiative for Asthma (GINA) guidelines recommend high-dose ICS-inhaled long-acting beta-agonist (LABA) therapy/add-on therapy with a biologic agent or tiotropium may be considered after phenotypic assessment. [11]
    * In patients with severe eosinophilic phenotype asthma uncontrolled on STEP 4-5 treatment, Nucala (mepolizumab), Cinqair (reslizumab), Fasenra (benralizumab), or Dupixent (dupilumab) are recommended as add-on treatment options. [12]
    * In patients with IgE-mediated allergic phenotype asthma uncontrolled on STEP 4-5 treatment, Xolair (omalizumab) is recommended as add-on therapy. [12]
    * In patients with severe asthma, regardless of phenotype, on STEP 4-5 treatment, Tezspire (tezepelumab-ekko) is recommended. [13]
- There is insufficient evidence that any one monoclonal respiratory antibody for uncontrolled asthma is superior to another. There are no comparative trials. Based on indirect trial comparisons, the benefits are roughly equivalent (rate of exacerbations).

Chronic Idiopathic/Spontaneous Urticaria (CIU/CSU) (Xolair)

- Xolair (omalizumab) may be coverable for poorly controlled chronic idiopathic urticaria despite use of maximal step therapy, which includes patient compliance with antihistamines and an assessment for other causes, including triggers, as well as a plan to control identified triggers.
- Standard of care for chronic urticaria includes identification and elimination of the underlying aggravating triggers followed by use of antihistamines. [14]
- Other potential therapies include leukotriene antagonists (such as montelukast), cyclosporine, dapsone, other oral DMARDs, and corticosteroids.
- All patients in Xolair (omalizumab) urticaria clinical trials of were refractory to antihistamines.
- The goal of CIU therapy is to decrease functional impairment due to itching, hives, and other related symptoms, such as missed days from work and/or school.

Eosinophilic granulomatosis with polyangiitis (EGPA) (Nucala)

- Nucala (mepolizumab) may be coverable when specific diagnostic criteria for EGPA are met and persistent disease despite use of maximal step therapy, which includes steroids and immunosuppressants (oral DMARDs).
- Glucocorticoids are the mainstay of therapy for EGPA. [15 16] Patients in clinical trials of Nucala (mepolizumab) for EGPA were relapsing or refractory to corticosteroids with or without immunosuppressives.
- Immunosuppressive oral DMARD therapy [e.g., azathioprine, methotrexate] is used as add-on therapy for patients with life and/or organ manifestations for maintenance of remission.
- There are still no trials comparing the effectiveness of Nucala (mepolizumab) to that of oral DMARD therapy in patients with EGPA, and 55% of patients in the MIRRA trial were on a non-steroid immunosuppressant.
- The American College of Rheumatology (ACR) recommend Nucala (mepolizumab) in combination with glucocorticoids as first line treatment for EGPA over oral DMARDS. However, oral DMARDS have a long-standing track record as an established treatment option for EGPA, are still recommended by the current ACR guidelines, and are a more cost-effective option.
- Other second line therapy options for EGPA include rituximab, immunoglobulins, and interferon-alpha.

Hypereosinophilic Syndrome (HES) (Nucala)

- Nucala (mepolizumab) may be coverable for uncontrolled HES (FIP1L1-PDGFRA–negative) despite stable background therapy for HES.
- Standard treatments for HES include oral corticosteroids, hydroxyurea, other cytotoxic therapy for HES (e.g., chlorambucil, vincristine), or interferon alpha.

Nasal Polyps

- Xolair (omalizumab) and Nucala (mepolizumab) may be coverable for nasal polyps in patient who have continued symptoms and quality of life impacts despite standard management.
- Standard treatments for nasal polyps include oral corticosteroids and intranasal corticosteroids (INCS).
- Initial coverage authorization is 24 weeks, per current guidelines to reassess effectiveness outlined in coverage criteria, as CRSwNP symptoms can resolve or medication may not provide adequate benefit.
- Monoclonal respiratory antibodies may be covered at the doses proven to be safe and effective for asthma and other associated conditions in clinical trials (as detailed in the coverage criteria above).

IgE-Mediated Food Allergy

- Xolair (omalizumab) may be coverable for confirmed multiple, severe IgE-mediated food allergy, as outlined in coverage criteria, when used conjunction with ongoing food allergen avoidance.

- The goal of treatment with Xolair (omalizumab) is the reduction of severe allergic reactions, including anaphylaxis, from accidental food allergen exposure, by increasing the tolerance or sensitivity threshold to the allergen(s). However, at this time, the evidence is limited to increase in allergic reaction threshold, based on tolerance of a single dose of peanut protein without dose-limiting symptoms. It is unknown if Xolair (omalizumab) will reduce the incidence of severe reactions with real-world food allergen exposure, use of rescue epinephrine, need for emergency medical care (such as ED visits), or improve quality of life.
- Confirmation of food allergens: Given complexity of food allergen evaluation, all patients should be evaluated by a specialist. Confirmatory tests used to diagnose food allergies include a skin prick test, an allergen specific IgE blood test, and an oral food challenge to the offending allergens, interpreted by a specialist, *in conjunction with* a medical history of a true food allergic reaction. True food allergies are defined by moderate to severe reactions affecting the skin, respiratory tract, gastrointestinal tract, or cardiovascular system. A positive diagnostic test, in the absence of a clinical history of a true allergic reaction, is not, by itself, indicative of a true allergy to the offending food allergen(s).
- Ongoing food allergen avoidance: Standard management is strict food allergen avoidance and the availability of rescue epinephrine for as-needed use with accidental food allergen exposure. Ongoing food allergen avoidance is required when using Xolair (omalizumab).

<u>Self-administration</u>

- Several options are now available in a single-dose pre-filled syringe (PFS) or autoinjector, FDA-approved for self-administration, and coverable under the pharmacy benefit, as detailed in the coverage criteria.
- Use of self-administered options provides the best value (lower overall cost) and may offer convenience for members.
- Provider-administered products may be needed when there is a documented reason why a patient cannot self-administer a medication (see *Appendix 5*).

The safety and efficacy of monoclonal respiratory antibodies in combination with other monoclonal respiratory antibodies or in conditions not included in coverage criteria (as listed above) have not been established. There are no trials of the use of anti-asthma monoclonal antibodies as combination or sequential therapy. Additional trials are ongoing.

Clinical Efficacy

ASTHMA BACKGROUND

- Asthma is a chronic inflammatory disorder of the airways in which many cells and cellular elements (multiple cytokines and mediators, as well as potentially IgE-mediated events involving mast cells and basophils) play a role (in particular, mast cells, eosinophils, T lymphocytes, macrophages, neutrophils, and epithelial cells). Eosinophilic asthma is a subphenotype of severe asthma characterized by elevated sputum and blood eosinophil levels as well as increased asthma severity, atopy, late-onset disease, and steroid refractoriness.
- IgE may be in the inflammatory cascade of some events leading to asthmatic airway inflammation. Anti-IgE monoclonal antibody, Xolair (omalizumab) binds circulating IgE.

- Anti-IL-5 monoclonal antibodies (Cinqair, Nucala, and Fasenra) specifically target formation of eosinophils and depletes blood eosinophil levels.
- Various peripheral blood eosinophil levels were studied in clinical trials. The eosinophil levels in the coverage criteria for the anti-IL-5 monoclonal antibodies are based on the efficacy data from the clinical trials of these medications and where they were found to be most effective.
- Global Initiative for Asthma (GINA) guidelines recommend STEP 5 add-on therapy with long-acting muscarinic antagonists (LAMA) such as tiotropium, anti-IgE therapy (omalizumab), anti-IL-5 therapy, anti-TSLP, or anti-interleukin-4 therapy after phenotypic assessment of asthma subtype. [17]
- There is no reliable evidence to establish efficacy or safety of monoclonal anti-IL-5 antibodies for severe allergic asthma without documentation of severe eosinophilia. [3]
- TSLP is a cytokine that is thought to stimulate the immune cascade response in epithelial cells leading to asthmatic airway inflammation. Anti-TSLP monoclonal antibody Tezspire (tezepelumab-ekko) blocks the TSLP cytokine to reduce the epithelial inflammatory response. [10]
- Tezepelumab has demonstrated efficacy in patients regardless of eosinophils or IgE levels. [18 19]

Fasenra (benralizumab) for Eosinophilic Asthma

- Two randomized, double-blinded, placebo-controlled studies (SIROCCO and CALIMA) evaluated the safety and efficacy of Fasenra (benralizumab) 30 mg in patients with severe eosinophilic asthma, uncontrolled on moderate- to high-doses ICS. [20 21]
    * The trials enrolled patients with a history of two or more asthma exacerbations requiring oral or systemic corticosteroid treatment in the past 12 months despite medium to high dose ICS/LABA. Patients were stratified by baseline blood eosinophil count (<300 or ≥300 cells/microliter).
    * The primary endpoint was reduction in asthma exacerbations for patients with baseline blood eosinophil count ≥300 cells/microliter in both studies. After 48-56 weeks, Fasenra (benralizumab) reduced the annual rate of exacerbations by 28-51% compared to placebo.
    * However, in the SIROCCO trial, only patients with a baseline blood eosinophil count ≥300 cells/microliter responded to the standard starting dose of Fasenra (benralizumab) 30 mg every 8 weeks. For patients with baseline blood eosinophil count <300 cells/microliter, response was seen only with double the dose (30 mg every 4 weeks).
- In CALIMA, patients on medium-dose ICS/LABA were included. Therefore, the generalizability of the results to patients optimized on standard STEP 5 therapy with high-dose ICS/LABA is uncertain. One double-blind, multicenter, randomized study evaluated the efficacy of Fasenra (benralizumab) on oral corticosteroid (OCS) reduction compared to placebo. [22]

    - Patients were required to have a daily oral corticosteroid dose between 7.5 to 40 mg per day in addition to high dose ICS/LABA and a baseline eosinophil count of at least 150 cells/microliter.
    - Patients in the Fasenra (benralizumab) arms (30 mg every 4 weeks or every 8 weeks) had a statistically significant reduction in daily OCS compared to placebo (75% vs. 25%, respectively). However, the external validity of the results is uncertain, given the inclusion of patients on medium-dose ICS/LABA.

- The role of Fasenra (benralizumab) for patients with a baseline blood eosinophil count of <300 cells/microliter is unclear. The overall assessment of benefit is uncertain, with inconsistent response to standard starting dosing and confounded baseline characteristics. Patients in two of the three trials were <u>not</u> on optimized high-dose ICS/LABA, as is the standard STEP5 (NHLBI and GINA guidance), prior to addition of anti-IL5 therapy.
    - In the SIROCCO trial, patients were optimized on high dose ICS/LABA. However, there was no statistical reduction in the rate of asthma exacerbations for patients with baseline blood eosinophil count of <300 in the arm of Fasenra (benralizumab) 30 mg every 8 weeks. Benefit was seen only at higher dosing (30 mg every 4 weeks). As such, Fasenra (benralizumab) if coverable only for patients with baseline blood eosinophil count of ≥300 cells/microliter. [Bleeker, PMID: 27609408]
    - In the CALIMA and ZONDA trials, there was statistically significant response to standard Fasenra (benralizumab) 30 mg every 8 weeks. However, patients were NOT optimized on high-dose ICS/LABA prior to enrollment. Both studies included patients on medium dose ICS/LABA, which is not reflective of Step 5 of NHLBI Guidelines for add-on IL-5 therapy. Therefore, the benefit in optimized Step 5 asthma patients with an eosinophil count of <300 is unknown.
        - In CALIMA, there was a statistically significant reduction in asthma exacerbation rates for patients with baseline blood eosinophil count of <300 cells/microliter in the arm of Fasenra (benralizumab) 30 mg every 8 weeks; however, because baseline ICS/LABA was not maximized, the external validity of this finding for use in a STEP5 therapy optimized patient is unknown. [Fitzgerald, PMID 27609406]
        - In ZONDA, there was a statistically significant reduction in the need for oral steroids for patients with baseline blood eosinophil count of >150 cells/microliter with Fasenra (benralizumab); however, because baseline ICS/LABA was not maximized, the external validity of this finding for use in a STEP 5 therapy optimized patient is unknown. [Nair, PMID 28530840]

<u>Nucala (mepolizumab) for Eosinophilic Asthma</u>

- One randomized, double-blinded, placebo- and active-controlled, 32-week study evaluated the safety and efficacy of Nucala (mepolizumab) 75 mg or 100 mg compared to placebo in patients with severe refractory eosinophilic asthma. [23]
    - The trial enrolled patients with blood eosinophil counts ≥150 cells/microliter within 6 weeks of dosing or ≥300 cells/microliter within 12 months.

    - The primary endpoint was frequency of asthma exacerbations. Nucala (mepolizumab) demonstrated a statistically significant reduction of annual exacerbation rates by 13% compared to placebo.
- One randomized, controlled trial evaluated the efficacy of Nucala (mepolizumab) in reducing daily oral corticosteroid dose compared to placebo. [24]
    - The primary end point was percent reduction of oral corticosteroid dose during weeks 20 to 24 without loss of asthma control. Overall, Nucala (mepolizumab) achieved greater reduction in oral corticosteroid use while maintaining asthma control when compared to placebo. However, the difference between the Nucala (mepolizumab) and placebo groups was not statistically significant.
- Nucala (mepolizumab) has been studied in moderate persistent asthma, and no significant benefit was observed. [25]

Xolair (omalizumab) for Extrinsic (allergic) Asthma

- One high-quality meta-analysis evaluated the efficacy of Xolair (omalizumab) in reducing asthma exacerbations and corticosteroid use compared to placebo.
    - After 16 to 60 weeks, Xolair (omalizumab) reduced asthma exacerbations from 26% to 16% of patients suffering from an exacerbation.
    - An absolute reduction in hospitalization risk was reduced from 3% to 0.5% with Xolair (omalizumab) over 28 to 60 weeks.
- Xolair (omalizumab) increases the number of asthma patients able to reduce or withdraw their inhaled steroids and is effective in reducing asthma. [26-29]
- There is no available data demonstrating that Xolair (omalizumab) is superior to step therapy options (e.g., ICS/LABAs and oral steroids for exacerbations) recommended in treatment guidelines for moderate-to-severe persistent asthma.
- Optimal clinical response to Xolair (omalizumab) requires strict compliance with dosing, as there is a 6 to 12-week lag before beneficial effects are apparent (effects are not immediate and explain the various phases that are included in study protocols).
- Although preliminary results are promising, there is no conclusive evidence that omalizumab is effective in patients with non-allergic (nonatopic) asthma, based on one small proof-of-concept trial. [30]

Total IgE Levels for Asthma

- Xolair (omalizumab) is only indicated in patients with elevated IgE levels and is dosed according to IgE levels between 30 to 700 IU/ml in adults with asthma. [31] There is no established dose or benefit for IgE levels outside of this range.
- Efficacy and dosing of Xolair (omalizumab) in asthma patients (>50 kg) with IgE levels less than 30 or greater than 700 have not been established. [31] The majority of data on the use of Xolair (omalizumab) in patients with baseline IgE <30 or >700 IU/ml are limited to case reports with inconsistent results of effectiveness.
- There is evidence to support the safety and efficacy of Xolair (omalizumab) in patients aged 6 to less than 12 years old with a baseline IgE as follows:
    - >90 to 150 kg: baseline IgE of 30 to 300 IU/ml

* >70 to 90 kg: baseline IgE of 30 to 500 IU/ml
* >60 to 70 kg: baseline IgE of 30 to 600 IU/ml
* >50 to 60 kg: baseline IgE of 30 to 700 IU/ml
* >40 to 50 kg: baseline IgE of 30 to 900 IU/ml
* >30 to 40 kg: baseline IgE of 30 to 1,100 IU/ml
* 20 to 30 kg: baseline IgE of 30 to 1,300 IU/ml

As with adults, there is no established dose or benefit for IgE levels outside of this range.

- Monitoring IgE levels after administration of Xolair (omalizumab) are problematic, as IgE levels post-administration measure both bound and unbound (free) IgE.

Cinqair (reslizumab) for Eosinophilic Asthma

- Cinqair (reslizumab) has been studied in people with moderate and severe refractory eosinophilic asthma that is inadequately controlled despite use of high-dose corticosteroids and a controller medication. [32-35]
- Two double-blind, controlled studies evaluated the efficacy of Cinqair (reslizumab) 3 mg/kg compared to placebo in patients with severe eosinophilic asthma. [35]
  * Patients were required to have at least 1 asthma exacerbation requiring systematic corticosteroids.
  * The primary endpoint was frequency of asthma exacerbation. After 52 weeks, Cinqair (reslizumab) reduced the annual asthma exacerbation rate by 10-14% compared to placebo.

Tezspire (tezepelumab-ekko) for Severe Asthma [10 18 19 36-39]

- One phase III, randomized, double-blinded, placebo controlled, 52-week study (NAVIGATOR) evaluated the safety and efficacy of Tezspire (tezepelumab-ekko) 210mg every 4 weeks compared to placebo in patients with severe asthma, uncontrolled on ICS/LABA therapy.
  * The trial enrolled patients who were previously diagnosed with asthma receiving a med/high dose ICS for the past 12 months (75% of patients were on high dose ICS in both arms) and secondary controller medication (LABA) for the past 3 months. Patients must have had a history of two or more asthma exacerbations (defined as requiring either oral/systemic corticosteroids or asthma related hospital stay) in the previous 12 months. Patients were stratified by baseline blood eosinophil count (<150, 150-300,300-450, and >450 cells/µL).
  * The primary endpoints were annualized asthma exacerbations rate (AAER) overall as well as in patients with blood eosinophil counts of ≤300 cells/µL. Tezspire (tezepelumab-ekko) demonstrated a statistically significant reduction in both overall annual exacerbation rates (56%) and in patients with blood eosinophil counts of ≤300 µL (41%) when compared to placebo.
  * Sub-group analysis of patients with blood eosinophils <150 cells/µL showed a statistically significant reduction in AAER by 39% when compared to placebo.
  * The above results were supported by similar findings in a previous phase IIB randomized placebo-controlled dose optimization trial (PATHWAY). In addition,

a sub-group analysis of patients with non-allergic asthma (IgE<30 IU/ml) showed a statistically significant reduction in AAER of 54% in this trial.

- One phase 3, randomized, double blind, placebo-controlled trial (SOURCE trial) evaluated the efficacy of Tezspire (tezepelumab-ekko) in reducing daily oral corticosteroid dose compared to placebo.
    * The primary end point was percent reduction of oral corticosteroid dose at week 48 without loss of asthma control. Overall, Tezspire (tezepelumab-ekko) achieved a greater reduction in oral corticosteroid use while maintaining asthma control when compared to placebo.
- Tezspire (tezepelumab-ekko) is the first monoclonal antibody to show statistically significant reductions in AAER in patients that have non eosinophilic asthma (blood eosinophils <150cells/µL) and in patients with non-allergic asthma (IgE<30 IU/ml).

CHRONIC IDIOPATHIC URTICARIA (CIU/CSU) BACKGROUND

- Standard of care includes identification and elimination of the underlying aggravating triggers followed by use of antihistamines, which are FDA-approved for treatment of urticaria and may be used at doses exceeding the manufacturer's recommended dosages. [14]
- Second-line treatment options for antihistamine-refractory urticaria include H2-antihistamines (e.g., ranitidine, famotidine), leukotriene antagonists, cyclosporine, dapsone, other oral DMARDs/anti-inflammatories (methotrexate, sulfasalazine), and corticosteroids. The guidelines acknowledge the evidence supporting the use of these second-line therapies is of lower quality; however, their costs and safety profiles should be considered when choosing therapies. [14]
- The terms "chronic urticaria" (CU), "chronic spontaneous urticaria" (CSU), and "chronic idiopathic urticaria" (CIU) are used interchangeably, but are generally defined as a frequent cause of severe chronic urticaria, lasting greater than 6 weeks. [14] However, in clinical trials, all patients had CIU/CSU symptoms for at least 6 months. [40-43]
- The diagnosis of "CIU/CSU" requires exclusion of triggers as a main cause of the urticaria symptoms, such as:
    * Physical causes [dermatographism (firm stroking), delayed pressure urticaria (pressure), cold urticaria (cold), solar urticaria (exposure to sun), or vibratory urticaria (vibration)].
    * Other causes [aquagenic urticaria (water exposure), cholinergic urticaria (heat, stress, exercise), exercise-induced anaphylaxis/urticaria, contact with urticariogenic substances].
    * Urticaria despite avoidance of any triggers is a hallmark feature of CIU/CSU. [14]
- In addition, spontaneous flares in the absence of a trigger must be documented to establish the diagnosis of spontaneous urticaria (CSU/CIU).
- A subset of patients with a diagnosis of CSU/CIU may have autoimmune urticaria, which can be associated with some type of trigger which can aggravate symptoms but is not the main cause of CU symptoms. Aggravating triggers may include but are not limited to extreme hot or cold, and irritation from clothing. Primary treatment for CU

should include aggravating trigger control and histamine blockade. Refractory patients may be responsive to Xolair (omalizumab). [14 41 42]

Xolair (omalizumab) for CIU/CSU

- Two randomized, double-blinded, placebo-controlled 12- to 24-week studies evaluated the safety and efficacy of Xolair (omalizumab) in patients with refractory chronic idiopathic/spontaneous urticaria. [41 44]
    - The trial enrolled patients with a urticaria activity score (UAS) >4 despite use of H1-antihistamines and a weekly itch severity score (ISS) >8.
    - Xolair (omalizumab) doses of up to 300 mg every 4 weeks were used.
    - The primary endpoint of the study was change from baseline in weekly ISS at week 12. Additional endpoints included the change in UAS over 7 days and proportion of complete responders.
    - Mean change in weekly ISS with Xolair (omalizumab) decreased by -3.0 from placebo. Although, this is a subjective endpoint with a lack of defined minimal clinically important difference, it is clinically relevant to patients. The FDA recognizes reduction of itching as the most important outcome.
- Xolair (omalizumab) may reduce urticaria severity, as measured by itch-severity score, in patients with chronic idiopathic urticaria who remained symptomatic despite use of H1-antihistamine therapy. However, Xolair (omalizumab) has not been proven to eliminate itching or improve functional impairment due to urticaria symptoms. [14 41-43]
- Xolair (omalizumab) has only been studied as add-on therapy in patients who are refractory to antihistamines.
    - Guidelines recommend use of maximally tolerated doses of non-sedating (2nd generation) antihistamines, up to four-times the recommended FDA-approved doses. [14]
    - All patients in clinical trials of Xolair (omalizumab) for chronic urticaria were refractory to antihistamines. [14] However, Xolair (omalizumab) has not been compared to the many other available therapies for antihistamine-refractory urticaria. Therefore, it is unknown if Xolair (omalizumab) is superior to these less-costly alternatives.
- IgE levels are not measured nor used as a marker for Xolair (omalizumab) therapy with urticaria.
- Urticarial flares may also occur in the presence of a trigger ("inducible urticaria"). However, patients may have a mixed diagnosis of CSU/CIU, along with inducible urticaria. Spontaneous flares, in the absence of a trigger, must be documented to establish the diagnosis of spontaneous urticaria (CSU/CIU).
- The efficacy or safety of Xolair (omalizumab) in other types of urticaria with a clearly defined cause, such as physical (inducible) urticaria (e.g., "cold" urticaria, dermographism, delayed-pressure urticaria, cholinergic urticaria, aquagenic urticaria, solar urticaria, or vibratory urticaria), urticarial vasculitis, or contact urticaria, has not been established. [14 43 45]

* Patients with a clearly defined cause for urticaria, such as physical cause, were excluded from CIU/CSU phase 3 clinical trials. [14 41-43]
* Avoidance of the stimulus is the primary treatment for physical (inducible) urticaria. Other treatments vary, dependent on the trigger, but may include antihistamines, steroids, desensitization protocols, and immunomodulators (such as cyclosporine). [46]
* Two small phase 2 trials investigated Xolair (omalizumab) in patients with cold and solar urticaria refractory to antihistamines.
    - CUTEX (n=30): [45] Patients with refractory cold urticaria were randomized to 150 mg, 300 mg, or placebo every 4 weeks. The primary endpoint was the individual temperature required to induce symptoms [critical temperature threshold (CTT)]. Although the CTT reduced in the treatment period, the benefit on health outcomes (such as systemic reactions and anaphylaxis) is unknown.
    - XOLUS (n=10): [47] Patients with refractory solar urticaria [to photoprotection (SPF 50 sunscreen) and antihistamines] were treated with Xolair (omalizumab) 300 mg every 4 weeks. The primary endpoint was response to therapy, measured by the percent of patients without urticaria triggering with exposure to UV light (10-times baseline level). Two of 10 met the primary endpoint. However, the benefit on health outcomes (such as systemic reactions and anaphylaxis) is unknown.
    - Additional trials are needed to clarify the benefit of Xolair (omalizumab) in refractory cold and/or solar urticaria. Of note: both of these trials were published as a 'letter to the editor' and were not peer-reviewed.
* The published evidence for the use of Xolair (omalizumab) in other types of physical (inducible) urticaria is limited to case reports. [46]

EOSINOPHILIC GRANULOMATOSIS WITH POLYANGIITIS (EGPA) BACKGROUND

- Eosinophilic granulomatosis with polyangiitis (EGPA), also known as allergic granulomatosis or Churg-Strauss syndrome, is a multisystem autoimmune syndrome characterized by eosinophil-rich granulomatosis inflammation of microscopic vessels. The respiratory tract is typically affected, and EGPA commonly includes asthma among its manifestations; however, widespread manifestations are found, including neurological, cardiac, and renal involvement.
- Classification of EGPA is most often according to 1990 classification criteria from the American College of Rheumatology. Patients with vasculitis may be classified as having EGPA if they have at least 4 of 6 typical findings: [48]
    * Asthma (a history of wheezing or finding or diffuse high-pitched wheezes on expiration).
    * Greater than 10 percent eosinophils on the differential leukocyte count.
    * Mononeuropathy (including multiplex) or polyneuropathy.
    * Migratory or transient opacities detected radiographically.
    * Paranasal sinus abnormality.

    - Biopsy containing a blood vessel showing the accumulation of eosinophils in extravascular areas.

- The primary therapy for EGPA is systemic corticosteroids. An additional immunosuppressive agent (e.g., cyclophosphamide) is typically added for patients with more active or severe disease and in those whose disease flares with tapering of systemic glucocorticoids. Once remission is induced, patients can be switched to less toxic immunosuppressives, such as azathioprine or methotrexate, for maintenance therapy. Second or third-line drugs include rituximab, immunoglobulins, and interferon-alpha. [15 16]

Nucala (mepolizumab) for EGPA

- The MIRRA trial (multicenter, randomized, double-blind, controlled) evaluated the efficacy of Nucala (mepolizumab) 300 mg in patients with relapsing or refractory EGPA not optimally controlled with an oral corticosteroid with or without oral DMARDs compared to placebo. [7]
- The primary endpoint was total accrued weeks of remission. Nucala (mepolizumab) was found to result in significantly more weeks in remission than placebo (28% vs. 3% of patients had ≥24 weeks of accrued remission).
- After 48 weeks, 32% of Nucala (mepolizumab) patients remained in remission allowing for reduced corticosteroid use compared to 3% of placebo patients.
- Nucala (mepolizumab) has only been studied as add-on therapy for EGPA. It has not been compared to oral DMARDs for corticosteroid-refractory EGPA. Therefore, it is unknown if Nucala (mepolizumab) is superior to these less costly alternatives.
- The 2021 American College of Rheumatology (ACR) guidelines for EGPA recommend systemic steroids in combination with Nucala (mepolizumab) as first line treatment for patients with active non-severe disease over methotrexate (MTX), azathioprine (AZA) or mycophenolate (MMF), however this is based solely on Nucala (mepolizumab) having a randomized trial showing benefit in EPGA compared to only clinical experience and observational studies with MTX, AZA, and MMF. [49]
- There are no trials comparing efficacy of Nucala (mepolizumab) to that of MTX, AZA, or MMF in patients with EGPA, and 55% of patients in the pivotal MIRRA trial were on a non-steroid immunosuppressant such as MTX, AZA, or MMF. [49]
- These non-steroid immunosuppressants have demonstrated effectiveness in observational trials and well as in clinical experience, are still recommended and recognized as treatment options by the ACR guidelines, and are significantly less costly. Adverse effects may limit use in some patients, but monitoring can alleviate most adverse events. [49]

HYPEREOSINOPHILIC SYNDROME (HES) BACKGROUND [50 51]

- HES is a rare blood disorder. It occurs when an individual's blood has very high numbers of eosinophils. Eosinophils make their way into various tissues, causing inflammation and eventually organ dysfunction. The most commonly involved organs in HES include the skin, lungs, heart, and nervous system.
- In approximately 75% of cases, the underlying cause is unknown. However, recent advances have led researchers to believe that eosinophilia may be due to a variety of

causes including myeloproliferative disorders or other disorders that affect bone marrow (myeloproliferative HES), increased production of interleukin-5 (lymphocytic HES), or a mutation in an unknown gene passed genetically (familial HES).

- The goal of HES treatment is to reduce eosinophil levels in the blood and tissues, thereby reversing and preventing end organ tissue damage, especially in the heart.
- For imatinib-sensitive HES variants (including those associated with the FIP1-like-1-platelet-derived growth factor receptor a fusion gene [FIP1L1-PDGFRA]), tyrosine kinase inhibitors such as imatinib (generic, Gleevec) are used for controlling malignant cell growth. [50 51]
- For all other types of HES (including FIP1L1-PDGFRA-negative HES), standard HES treatment includes: [50 51]
    * First line: corticosteroids such as prednisone
    * Steroid-sparing and second line options: immunosuppressives and chemotherapeutic agents such as cyclophosphamide, rituximab, imatinib (in select patients), vincristine, hydroxyurea, chlorambucil, interferon-alpha, and other kinase inhibitors (such as tofacitinib, ruxolitinib). Choice of treatment is dependent on presence/absence of myeloid features and suspected myeloid malignancy. In clinical trials, other steroid sparing therapies also included cyclosporine, imatinib, methotrexate, tacrolimus, and azathioprine. [52]
- At this time, Nucala (mepolizumab) is the only respiratory mAb with evidence for efficacy in HES as a steroid-sparing disease modifier. Trials of Fasenra (benralizumab) are ongoing. [4]

Nucala (mepolizumab) for HES

- The efficacy of Nucala (mepolizumab) in HES was evaluated in a phase 3, randomized, double-blind, placebo-controlled trial in patients with a diagnosis of FIP1L1-PDGFRA–negative HES ≥6 months (Study 200622). [52]
- All enrolled patients had FIP1L1-PDGFRA–negative HES.
- HES was required to be uncontrolled (defined as a history of ≥2 flares within the past 12 months and a blood eosinophil count ≥1000 cells/μL) despite stable background with HES therapy.
- Background HES therapy included at least four weeks on a stable dose of oral corticosteroids and/or various immunosuppressants/cytotoxic agents, including but not limited to hydroxyurea, cyclosporine, imatinib, methotrexate, tacrolimus, and azathioprine.
- Patients received treatment with mepolizumab or placebo, in addition to their existing HES therapy.
- The primary endpoint was the proportion of patients with 1 or more flares at the end of the 32-week study.
- At the end of the treatment period, less patients treated with Nucala (mepolizumab) experienced a flare compared to patients treated placebo (28% vs. 56%, respectively).

- Nucala (mepolizumab) has only been studied as add-on therapy for HES and has not been compared to other alternatives. Therefore, it is unknown if Nucala (mepolizumab) is superior to less costly alternatives.

CHRONIC RHINOSINUTISIS WITH NASAL POLYPS BACKGROUND[53-55]

- Chronic rhinosinusitis (CRS) is a common condition. It is defined as inflammation of at least one paranasal sinus. It is characterized as chronic when symptoms persist for at least 12 weeks. CRS is divided into CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP). Endoscopy or on a sinus computed tomographic (CT) is needed to confirm the diagnosis of nasal polyps.
- Symptoms of nasal polyps include chronic congestion, facial pressure, purulent postnasal drip, throat clearing, coughing, and reduced ability to smell.
- Oral corticosteroids and intranasal corticosteroids (INCS) are the mainstay of therapy. Oral corticosteroids decrease nasal polyp size but are not used long-term.
- INCS decrease polyp size and prevent recurrence in patients who have had polyps removed through surgery. INCS include those products for intranasal use specifically (such as sprays), as well as other steroid solutions (such as budesonide nebs, used intranasally) or surgically implanted steroid-eluding stents.

Xolair (omalizumab) for Nasal Polyps[56]

- The safety and efficacy of Xolair (omalizumab) for nasal polyps was established based on two phase 3 studies: POLYP-1 and POLYP-2.
- Both studies compared Xolair (omalizumab) in combination with mometasone fumarate nasal spray (MFNS) vs. MFNS alone.
- The studies included patients with bilateral polyposis that persisted despite treatment with oral corticosteroids.
- The primary endpoints were change in Nasal Polyp Score (NPS) and nasal congestion score (NCS). Secondary endpoints other measures such as polyp size, disease severity, and symptoms.
- Treatment with Xolair (omalizumab) with MFNS improved nasal polyp scores and improved symptoms compared to MFNS alone. Secondary endpoints also favored the Xolair (omalizumab) group.
- Xolair (omalizumab) is only indicated in patients with elevated IgE levels and is dosed according to IgE levels between 30 and 1600 IU/mL in patients with nasal polyps. There is no established dose or benefit for IgE levels outside of this range.

Nucala (mepolizumab) for Nasal Polyps[57]

- The safety and efficacy of Nucala (mepolizumab) for nasal polyps was established in one 52-week phase 3 study.
- The study compared Nucala (mepolizumab) in combination with MFNS versus MFNS alone.
- Patients were required to have had at least one surgery for nasal polyps in the past 10 years and must have received background nasal corticosteroids for at least 8 weeks prior to the study.

- The co-primary endpoints were change in total endoscopic Nasal Polyp Score (NPS) from baseline and change in mean nasal obstruction VAS score during weeks 49-52. Secondary endpoints included other measures such as polyp size, disease severity, and symptoms.
- Treatment with Nucala (mepolizumab) decreased the size of nasal polyps and improved nasal obstruction through 52 weeks. Treatment with Nucala (mepolizumab) also resulted in a longer time to nasal surgery (nasal polypectomy) compared to standard of care.

IgE-MEDIATED FOOD ALLERGY BACKGROUND[58 59]

- IgE-mediated food allergies typically develop within seconds or minutes after ingestion of the culprit food with widespread activation of immune cells, which are responsible for the accompanying allergic symptoms--the most life-threatening being anaphylaxis.
- IgE-mediated allergic symptoms usually involve more than one organ system, and may include severe airway problems (bronchospasm, angioedema), hypotension, severe gastrointestinal symptoms (nausea, vomiting), and skin reactions (urticarial rash, erythema, flushing).
- Given the complexity of assessment of allergic reactions, a full evaluation by a clinical specialist (such as an allergist/immunologist) is recommended.
- The diagnosis of an IgE-mediated food allergy is confirmed by a positive result of at least one of the following allergy-diagnostic tests, in combination with a history of a food-related allergic reaction to the suspected foods:
- Skin prick test (SPT)
- Allergen-specific IgE test
- Double-blind oral-food challenge to the offending food(s) [gold standard].

  The many other non-standardized testing methods are considered non-confirmatory. [59]
- Avoidance of culprit food allergens to decrease the risk of allergic reactions is the preferred strategy outlined in guidelines, in addition to as-needed antihistamines (diphenhydramine) and epinephrine use for the treatment of an acute allergic reaction.
- Desensitization: Current guidelines do not recommend the use of oral immunotherapy (OIT) as a treatment approach for severe food allergy. However, the guidelines have not been recently updated (2011) and many allergists/immunologists use OIT as part of comprehensive management of allergies, when appropriate.

Xolair (omalizumab) for IgE-Mediated Food Allergies[60]

- The safety and efficacy of Xolair (omalizumab) for reduction of food allergy reactions was evaluated in one 16-week, phase 3 randomized, double blind, placebo-controlled trial in 168 patients with moderate-to-severe food allergies (of which 165 were pediatric).
- All subjects had an allergy to peanut plus at least two other foods, including milk, egg, wheat, cashew, hazelnut, and/or walnut.

- All food allergies were confirmed by all of the following positive diagnostic tests:
  * Skin prick test (SPT) defined as ≥ 4mm wheal greater than saline control to allergen.
  * Allergen specific immunoglobulin, IgE, ≥ 6kUA/L determined by ImmunoCAP.
  * Double blinded placebo-controlled food challenge (DBPCFC) defined as experiencing dose-limiting symptoms at a single dose of ≤ 100mg of peanut protein or ≤ 300mg of other above-listed allergen protein [100mg of peanut protein is the equivalent of 1/2 of a peanut].
  * Use of Xolair (omalizumab) for treatment of food allergy determined by tests (other than listed in the coverage criteria) is considered investigational and not coverable.
- All subjects had a moderate-to-severe peanut allergy, defined as:
  * Dose-limiting food allergy symptoms to a single dose of 100mg or less of peanut protein (equivalent to one-half of a peanut) and 300mg or less of protein for each of the other six foods at baseline.
- Moderate to severe symptoms including skin, respiratory, and/or gastrointestinal (GI) symptoms.
  * The primary efficacy endpoint was the percentage of patients who were able to consume a single dose of 600mg or more of peanut protein at week 16 without dose-limiting symptoms.
    - At week 16, a higher percent of subjects in the Xolair (omalizumab) arm were able to consume at least 600mg of peanut protein as compared to placebo (68% vs. 5%, p<0.001).
    - The clinical meaningfulness of the primary endpoint is unknown, as the 600 mg dose is a small amount of peanut protein relative to what may be consumed during an accidental exposure [600 mg is the equivalent to three whole peanuts or one-half teaspoon of peanut butter]. It is unknown if this endpoint predicts the clinically meaningful outcomes, such as reduced healthcare utilization, reduction in fatal anaphylaxis, need for rescue epinephrine use, or emergency department care.
    - Of note, 17% of subjects treated with Xolair (omalizumab) had no significant change in the amount of peanut protein tolerated. Therefore, the use of Xolair (omalizumab) for ongoing treatment of IgE-mediated food allergies is coverable only when there is a reduction in the frequency or severity of food allergic reactions, and need for additional medical care, as compared to baseline reactions.
  * Secondary endpoints included tolerance of a food challenge with a variety of other allergen food challenges (cashews, milk, egg), all of which met statistical significance in favor of omalizumab [≥ 1000mg cashew protein (~3.5 cashews), milk protein (~2 tablespoons of milk) or egg (1/4 of an egg)]. However, despite numerical trends of improvement, more adequately powered studies are needed to confirm any clinical utility of the use of Xolair (omalizumab) for other food allergies. On average, around 20% of subjects treated with Xolair (omalizumab) had no significant change in the amount of cashew, milk, or food protein tolerated.

- Clinically relevant outcomes for IgE-mediated food allergy, such as absence of any allergic reaction, reduced rates of hospitalizations or emergency department visits, reduction in rates of anaphylaxis, reductions in rates of epinephrine rescue use, or overall quality of life improvement were not evaluated in the pivotal trial.
- Use of Xolair (omalizumab) for food allergy has not been shown to reduce the need for additional medical care [such as emergency department (ED) use or epinephrine (EpiPen) use], induce permanent tolerance to allergens, or improve ability to eat an unrestricted diet. Because Xolair (omalizumab is not curative, treatment will require chronic administration, continuation of allergen avoidance, and availability of "as needed" epinephrine (EpiPen) rescue use for allergic reactions from accidental exposure.
- Investigational Uses:
    * In the pivotal trial for IgE-related food allergy, subjects aged 1 to 55 years old were eligible for enrollment in the trial. However, 165 of 168 enrolled subjects were pediatric (age 1 to 17) and the prespecified primary efficacy analysis population. At this time, there is insufficient evidence to establish the safety, efficacy, or dosing of Xolair (omalizumab) for IgE-mediated food allergy in adults. Therefore, the use of Xolair (omalizumab) in adults (≥ 18 years old) with IgE-mediated food allergy is considered investigational.
    * All patients in the available trial(s) had a confirmed peanut allergy along with at least two other food allergies. Therefore, there is insufficient evidence to establish the efficacy of Xolair (omalizumab) in patients without a documented peanut allergy OR in patients with isolated peanut allergy. The use of Xolair (omalizumab) in patients with isolated peanut allergy is not supported by the available published clinical trial evidence.

Not Medically Necessary Uses

- Xolair (omalizumab) reduces seasonal and perennial allergic rhinitis symptoms but has not been shown to have better efficacy than first-line alternatives, such as nasal corticosteroids, antihistamines, or allergen desensitization therapy. [61-63]
- There is interest in the use of other monoclonal antibodies for allergic rhinitis, such a mepolizumab (Nucala). However, there is insufficient evidence to establish benefit versus the many available lower cost treatment options. [64]

Safety

- All monoclonal antibodies for asthma have a theoretical risk of opportunistic infections (including parasitic infections) and malignancy. Immunogenicity and development of antidrug antibodies was observed in clinical trials of Nucala (mepolizumab) and Cinqair (reslizumab). [65 66]
- Anaphylaxis is a concern with administration of anti-asthma monoclonal antibodies. Xolair (omalizumab) FDA labeling details assessment of risk for anaphylaxis (see *Appendix 5*).
- The safety and effectiveness of dose escalation for patients not responding to standard doses have not been established.

Appendix 1: Low, Medium, and High Daily Doses of Inhaled Corticosteroids (Adapted from GINA 2019 Guidelines) [12]

Adults and Adolescents (Age 12 years and Older)				
Drug	**Products**	**Daily Dose**		
		Low	**Medium**	**High**
Beclomethasone dipropionate (CFC)	None	200-500	>500-1000	>1000
Beclomethasone dipropionate (HFA)	QVAR Redihaler	100-200	>200-400	>400
Budesonide (DPI)	- Symbicort - Pulmicort Flexhaler	200-400	>400-800	>800
Ciclesonide (HFA)	Alvesco	80-160	>160-320	>320
Fluticasone furoate (DPI)	- Breo Ellipta - Arnuity Ellipta - Trelegy Ellipta	100	N/A	200
Fluticasone propionate (DPI)	- Advair Diskus - Flovent Diskus - Wixela Inhub - AirDuo RespiClick - ArmonAir RespiClick	100-250	>250-500	>500
Fluticasone propionate (HFA)	- Advair HFA - Flovent HFA	100-250	>250-500	>500
Mometasone furoate	- Dulera - Asmanex	110-220	>220-440	>440
Triamcinolone acetonide	Azmacort	400-1000	>1000-2000	>2000

Key: DPI: dry power inhaler; HFA: hydrofluoroalkane.

Children age 6-11 years				
Drug	**Products**	**Daily Dose**		
		Low	**Medium**	**High**
Beclomethasone dipropionate (CFC)	None	100-200	>200-400	>400
Beclomethasone dipropionate (HFA)	QVAR Redihaler	50-100	>100-200	>200
Budesonide (DPI)	- Symbicort - Pulmicort Flexhaler	100-200	>200-400	>400
Ciclesonide (HFA)	Alvesco	80	>80-160	>160
Fluticasone furoate (DPI)	- Breo Ellipta - Arnuity Ellipta - Trelegy Ellipta	N/A	N/A	N/A
Fluticasone propionate (DPI):	- Advair Diskus - Flovent Diskus - Wixela Inhub - AirDuo RespiClick - ArmonAir RespiClick	100-200	>200-400	>400
Fluticasone propionate (HFA)	- Advair HFA - Flovent HFA	100-200	>200-500	>500
Mometasone furoate	- Dulera - Asmanex	110	≥220-<440	≥440
Triamcinolone acetonide	Azmacort	400-800	>800-1200	>1200

Key: DPI: dry power inhaler; HFA: hydrofluoroalkane.

Children age 0-5 years		
Drug	**Products**	**Daily Dose**
		Low
Beclomethasone dipropionate (HFA)	QVAR Redihaler	100 (ages ≥5 years)
Budesonide nebulized	Generic	500 (ages ≥1 years)
Budesonide pressurized MDI	Pulmicort Flexhaler	Not sufficiently studied in this age group
Ciclesonide (HFA)	Alvesco	Not sufficiently studied in this age group
Fluticasone propionate (HFA)	Flovent HFA	50 (ages ≥4 years)
Mometasone furoate	Asmanex	110 (ages ≥4 years)
Triamcinolone acetonide	Azmacort	Not sufficiently studied in this age group

Key: DPI: dry power inhaler; HFA: hydrofluoroalkane.

Appendix 2: Inhaled Corticosteroid/Long-acting Beta-agonist (ICS/LABA) Combinations

Product	Dosing	Max Puff/Day	High Dose?	Available Strength [a]
Fluticasone propionate/salmeterol DPI (Advair Diskus)	Twice daily	2 (1,000 mcg)	Yes (>500)	100/50 250/50 500/50
Fluticasone propionate/ salmeterol MDI (Advair HFA)	Twice daily	4 (920 mcg)	Yes (>440)	45/21 115/21 230/21
Budesonide + formoterol MDI (Symbicort)	Twice daily	4 (640 mcg)	No[a]	80/4.5 160/4.5
Fluticasone propionate / salmeterol DPI (AirDuo RespiClick)	Twice daily	2 (464 mcg)	No[b]	55/14 113/14 232/14
Mometasone/ formoterol MDI (Dulera)	Twice daily	4 (800 mcg)	Yes (>400)	100/5 200/5
Fluticasone furoate/vilanterol DPI (Breo Ellipta)	Once daily	1 (200 mcg)	Yes (>200)	100/25 200/25

[a] High dose budesonide is >1,200 mcg/day. Maximum daily dose of budesonide from Symbicort (budesonide/formoterol) is 640 mcg/day, a medium dose of ICS.

[b] High dose fluticasone propionate DPI is >500 mcg/day. Maximum daily dose of fluticasone propionate from AirDuo RespiClick (fluticasone propionate/salmeterol DPI) is 464 mcg/day, a medium dose of ICS.

Appendix 3: Antihistamines

H_1-Antihistamines

First Generation (non-selective, "sedating")

- brompheniramine
- chlorpheniramine (generic Chlor-Trimeton)
- clemastine (generic Tavist)
- cyproheptadine (generic Periactin)
- dexbrompheniramine
- dexchlorpheniramine
- diphenhydramine (generic Benadryl)
- hydroxyzine (generic Vistaril)

Second Generation (peripherally-selective, "non-sedating")

- cetirizine (generic Zyrtec)
- desloratadine (Clarinex)
- fexofenadine (generic Allegra)
- levocetirizine (Xyzal)
- loratadine (generic Claritin)

H_2-Antihistamines

- cimetidine (generic Tagamet)
- famotidine (generic Pepcid)
- nizatidine (generic Axid)
- ranitidine (generic Zantac)

Appendix 4: Steroid-sparing therapies for Hypereosinophilic syndrome (HES) [50-52]
Immunosuppressives and chemotherapeutic agents: - cyclophosphamide - rituximab - imatinib (in select patients) [a] - vincristine - hydroxyurea [a] - chlorambucil - interferon-alpha - other kinase inhibitors (such as tofacitinib, ruxolitinib) - cyclosporine [a] - methotrexate [a] - tacrolimus [a] - azathioprine [a] - alemtuzumab - Other: cladribine, etoposide, mycophenolate mofetil (MMF)

[a] One of the baseline HES therapies reported in the mepolizumab pivotal HES trial (Study 200622)

Appendix 5. Monoclonal antibodies for asthma and other immune conditions approved for self-administration – Examples of Medical Rationale for Contraindications to Self-Injection	
For all self-administered options	
The healthcare provider determines self-injection is not appropriate, as documented by a medically justifiable rationale, such as: - Patient or patient's caregiver is not able to self-administer the prescribed monoclonal antibody as a PFS or autoinjector (Fasenra, Nucala, or Xolair) due to significant behavioral issues and/or cognitive impairment including, but not limited to, those associated with developmental delay, down syndrome, dementia, or excessive anxiety such as severe needle phobia, documented in the clinical records. - Prior severe infusion reactions - Medically unstable asthma, such as concurrent treatment with medications that require a higher level of monitoring (such as oxygen) or acute treatment of asthma despite maximal medical management.	
Product-specific contraindications	
Fasenra (benralizumab)[67]	None
Nucala (mepolizumab)[65]	Patient is less than 11 years of age (the 40 mg dose is not currently available as a self-administered formulation: PFS or autoinjector)
Xolair (omalizumab)[53]	Patient is higher risk of anaphylaxis (has known risk factors) - Prior history of anaphylaxis, including to Xolair (omalizumab) or other agents, such as foods, drugs, biologics, etc. - History of hypersensitivity reactions to Xolair (omalizumab). - Patient or caregiver is NOT able to recognize symptoms of anaphylaxis and treat anaphylaxis appropriately.

PFS = pre-filled syringe

Appendix 6. Monoclonal Antibodies and Targeted Immunomodulators for Asthma and other Autoimmune (Inflammatory) conditions
Fasenra (benralizumab)
Dupixent (dupilumab) [refer to Dupixent, dupilumab, Medication Policy Manual, Policy No. dru493]
Nucala (mepolizumab)
Cinqair (reslizumab)
Xolair (omalizumab)
Tezspire (tezepelumab-ekko)
Targeted immunomodulators Antibodies for CID [refer to Drugs for chronic inflammatory diseases, Medication Policy Manual, Policy No. dru444]

Cross References
Allergy Testing lab01, TRG Medical Policy Manual, Laboratory
Implantable Sinus Devices for Postoperative Use Following Endoscopic Sinus Surgery and for Recurrent Sinonasal Polyposis SUR198, TRG Medical Policy Manual, Surgery
Non-Preferred Inhaled Corticosteroid-Containing Medications, Medication Policy Manual, Policy No. dru380
Dupixent, dupilumab, Medication Policy Manual, Policy No. dru493
Drugs for chronic inflammatory diseases, Medication Policy Manual, Policy No. dru444
Site of Care Review, Medication Policy Manual, Policy No. dru408
Palforzia, peanut (Arachis hypogaea) allergen oral powder-dnfp, Medication Policy Manual, Policy No. dru634

Codes	Number	Description
HCPCS	J2182	Injection, mepolizumab (Nucala), 1 mg
HCPCS	J2357	Injection, omalizumab (Xolair), 5 mg
HCPCS	J2786	Injection, reslizumab (Cinqair), 1 mg
HCPCS	J0517	Injection, benralizumab (Fasenra), 1 mg
HCPCS	J2356	Injection, tezepelumab (Tezspire), 1 mg

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Revision History

Revision Date	Revision Summary
6/20/2024	• Added coverage criteria for a new indication for Xolair (omalizumab) for treatment of IgE-mediated food allergy. Limits coverage to patients with one or more food allergies, confirmed with allergy diagnostic testing and use in combination with ongoing food allergen avoidance (effective 9/1/2024). • Added Tezspire (tezepelumab) to site of care program (effective 10/1/2024).
12/7/2023	Removed monoclonal antibody step for Tezspire (tezepelumab) in severe asthma. Updated reauthorization criteria for operational consistency.
6/15/2023	• Clarification of steroid-sparing therapy step criteria for Nucala (mepolizumab) in hypereosinophilic syndrome (HES), for operational consistency (no change to intent). • Added Tezspire single-use autoinjector as a self-administered treatment option.
12/9/2022	• Reworded criteria for chronic idiopathic urticaria, (CIU) criteria for operational consistency (no change to intent). • Updated CIU/CSU reauthorization and quantity limit for patients with a partial response to Xolair (omalizumab), but persistent symptoms. • Added chronic eosinophilic pneumonia (CEP) and Hyper E Syndrome (HES) (except as listed in the coverage criteria) to the list of "Investigational Uses." • Clarified that allergic rhinitis is "Not Medically Necessary Uses" to include allergic rhinitis for all monoclonal antibody therapies in this policy.
6/17/2022	• Added coverage criteria for the newly FDA-approved drug Tezspire (tezepelumab-ekko). Limits coverage to patients with severe asthma when prescribed by a specialist, adherent use of ICS/ LABA has been ineffective, and blood eosinophils are less than 150 cells/ L. Additionally the asthma must be non-allergic, and the patient is not oral corticosteroid dependent. Step therapy with at least one monoclonal antibody for severe asthma is required. • Updated nasal polyp criteria for initial authorization to be at 24 weeks per guidelines, and continued reauthorization may be annually thereafter.

Revision Date	Revision Summary
3/18/2022	• Updated nasal polyp criteria to show that both Xolair (omalizumab) and Nucala (mepolizumab) require combination use of intranasal corticosteroids. IgE levels are only required for use of Xolair (omalizumab) in nasal polyps.
10/15/2021	• Added Site of Care (SOC) requirements for provider-administered doses. • Added coverage criteria for Nucala (mepolizumab) for nasal polyps and clarified severity criteria. • Updated benefit and administration language section.
4/21/2021	• Added coverage criteria for use of Nucala (mepolizumab) in hypereosinophilic syndrome (HES), a newly FDA approved indication. • Added coverage criteria for use of Xolair (omalizumab) in nasal polyps, a newly FDA approved indication. • Revised asthma criteria: - Changed requirement for previous courses of oral corticosteroids in past 12 months from two to one. - Simplified eosinophil count criteria for Fasenra (benralizumab), Nucala (mepolizumab), and Cinqair (reslizumab). - Removed requirement that smoking must have been discontinued. • Added Continuation of Therapy (COT) criteria • Updated "Investigational Uses" • Added Xolair pre-filled syringe as a self-administered treatment option.
10/23/2019	• Added Fasenra (benralizumab) and Nucala (mepolizumab) single-dose pre-filled autoinjector for self-administration to the policy. All other anti-asthma antibodies in the policy remain provider-administered only. Effective November 15, 2019: • Updated coverage criteria for asthma: - Clarified that maximally tolerated inhaled corticosteroid and long-acting inhaled beta-2 agonist therapy must have been tried. - Removed requirement for use of oral corticosteroids if exacerbations are present. - Revised definition of poor asthma control to include clarify requirement for two additional oral corticosteroid bursts or emergency department visits or hospitalizations.
4/25/2019	Updated and fixed incorrect references. No changes to policy criteria with this update.
1/31/2019	Clarified intent of trigger criteria.

Revision Date	Revision Summary
11/16/2018	Clarified intent of trigger, step therapy, quantity limit and reauthorization criteria.
3/16/2018	New policy: • The Xolair, Nucala, and Cinqair policies were combined. • Coverage criteria added for asthma for newly-approved Fasenra. • Coverage criteria added for EGPA for Nucala.

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Medication Policy Manual | **Policy No:** dru539

Topic: Hemlibra, emicizumab-kxwh | **Date of Origin:** May 1, 2018

Committee Approval Date: June 20, 2024 | **Next Review Date:** 2025

Effective Date: September 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Hemlibra (emicizumab-kxwh) is a monoclonal antibody used for patients with hemophilia A with or without factor VIII (FVIII) inhibitors. It is used for routine prophylaxis to prevent or decrease the frequency of bleeding episodes.

Policy/Criteria

Most contracts require pre-authorization approval of Hemlibra (emicizumab-kxwh) prior to coverage.

I. Continuation of therapy (COT): Hemlibra (emicizumab-kxwh) may be considered medically necessary for COT when criterion A **AND** B below is met.

A. One of the following (1 or 2):

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

OR

2. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

AND

B. "Administration, Quantity Limitations, and Authorization Period" below applies, as well as "Not Medically Necessary" for combination therapy and "Investigational Uses."

Please note: *Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve): Hemlibra (emicizumab-kxwh) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) confirming criterion A or B below are met.

A. **Hemophilia A with high titer FVIII inhibitors**, when criteria 1 and 2 below are met:

1. A diagnosis of **hemophilia A** (congenital FVIII deficiency), established by or in consultation with a hematologist.

AND

2. Documentation of a history of high anti-FVIII titer (≥5 Bethesda units).

OR

B. **Hemophilia A without FVIII inhibitors (also referred to "with low or no titer FVIII inhibitors")**, when criteria 1 and 2 below are met:

1. A diagnosis of **hemophilia A** (congenital FVIII deficiency), established by or in consultation with a hematologist.

AND

2. ONE of the following is met (a or b):

a. There is a documented objective clinical reason that all available lower-cost FVIII blood factor products are not appropriate (as listed in *Appendix 1*).

OR

b. Prophylactically administered lower-cost factor VIII products (as listed in *Appendix 2*) have been ineffective, as defined by the patient continuing to have documented (e.g., bleed diary or detailed provider notes) clinically significant bleeding events (such as target joint bleeds or other end-organ damage) despite adherent use doses of lower-cost factor VIII products (dose and dose frequency, as listed in *Appendix 2*).

PLEASE NOTE: On-demand ("PRN") use of a factor VIII product (short half-life or extended half-life) will not meet the intent of this efficacy criteria.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Hemlibra (emicizumab-kxwh) coverable under the medical benefit or pharmacy benefit. Determination of coverage under the pharmacy or medical benefit is based on group-specific benefits, as defined in the group and member contract (as determined by the member contract with the health plan, regardless of self- or provider-administration).

B. When pre-authorization is approved, Hemlibra (emicizumab-kxwh) will be authorized as follows:

1. In quantities up to 3 mg/kg per week for the first 4 weeks.

2. After the initial first four doses, quantities up to 1.5 mg/kg per week (based on dosing weekly 1.5 mg/kg every week, 3 mg/kg every two weeks, or 6 mg/kg every 4 weeks) may be authorized.

3. Doses authorized will be based on the closest available vial size.

4. Doses greater than listed above are considered investigational.

C. Authorization shall be reviewed as follows:

1. Hemlibra (emicizumab-kxwh) will be authorized for up to one year.

2. Authorization **shall** be reviewed at least annually to confirm that the medication continues to be effective.

IV. Hemlibra (emicizumab-kxwh) is considered investigational when used for all other conditions.

V. Use of Hemlibra (emicizumab-kxwh) in combination with prophylactic high-cost extended half-life (EHL) FVIII products (such as those *Appendix 3*) is considered "not medically necessary."

Position Statement

Summary

- Hemlibra (emicizumab-kxwh) is a humanized monoclonal modified antibody with a bispecific antibody structure binding factor IXa and factor X. It is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A (congenital factor VIII deficiency) with or without FVIII inhibitors (also referred to "low or undetectable titer FVIII inhibitors"). [1]
- The intent of the policy is to allow for coverage for Hemlibra (emicizumab-kxwh) for patients with hemophilia A for up to the FDA-approved dose, in the following patients:
  * Patients with high titer FVIII inhibitors (such that FVIII blood products would not be effective) or
  * When lower- cost FVIII blood products ("blood factor concentrates") are used but ineffective, such that a higher-cost longer-acting prophylactic hemophilia product is needed as detailed in the coverage criteria.
- In addition, the intent of the policy is to ensure ongoing use of Hemlibra (emicizumab-kxwh) is effective for reduction of bleeding and used in doses up to the coverable amount.
- Hemlibra (emicizumab-kxwh) was studied in four phase 3 trials in adult and pediatric patients with hemophilia A with or without FVIII inhibitors. It was shown to be safe and effective for reduction of bleeding in both types of patients.[1-4]
- Therapy should be individualized based on age, bleeding phenotype, weight, inhibitor status, history of bleeding episodes, and availability of factor concentrates. Patients with a suboptimal response to factor concentrates should be assessed for inhibitors.
- The primary goal of factor replacement therapy (with blood products or emicizumab) is to prevent bleeding and treat bleeding (with blood products only). A reduction in bleeding events and subsequent sequalae demonstrate the efficacy of treatment.
- Patients who continue to have spontaneous clinically significant bleeds (such target joint bleeds or other end-organ damage) or cannot maintain optimal factor levels despite adherence to adequate (FDA-recommended) doses of lower-cost factor VIII products may see benefit from higher-cost EHL FVIII products or Hemlibra (emicizumab-kxwh).
- Hemophilia A **with** FVIII inhibitors:
  * There are a limited number of treatment options for hemophilia A **with** FVIII inhibitors.
  * The Medical and Scientific Advisory Council (MASAC) states that the choice of product depends on multiple factors, including titer of inhibitor, bleed history, and previous response to products.[5]
- Hemophilia A **without** FVIII inhibitors:
  * However, there are numerous FVIII concentrate products (blood factor repletion with FVIII replacement products) available for management of hemophilia A patients without FVIII inhibitors (See *Appendices 2 and 3*).
  * FVIII concentrate products are effective for achieving hemostasis in patients without FVIII inhibitors, based on years of clinical experience.

* There is no head-to-head evidence that emicizumab prophylaxis is safer or more effective than blood product prophylactic regimens (SHL or EHL FVIII) in terms of annualized bleed rates (ABR). However, emicizumab and higher-cost EHL FVIII product prophylactic regimens are more costly than the lower-cost FVIII product prophylactic regimens. Therefore, emicizumab is coverable only when lower-cost FVIII products are ineffective, or all are medically contraindicated.

- Recommendations by the Medical and Scientific Advisory Council (MASAC) for the treatment of hemophilia without inhibitors recommends that providers discuss the risks and benefits of emicizumab compared to their existing therapy with patients, but MASAC does not endorse one treatment over another. There are numerous treatment options in this population and no distinction is made between different factor products. [6]
- Hemlibra (emicizumab-kxwh) may be covered for the dosing shown to be safe and effective in trials (up to 1.5 mg/kg every week after titration, or consolidated dosing every two or four weeks). The safety and effectiveness of higher doses have not been evaluated.[1]
- The safety and effectiveness of Hemlibra (emicizumab-kxwh) in conditions other than hemophilia A (with or without inhibitors) have not been established.
- Hemlibra (emicizumab-kxwh) is used for "baseline" prophylaxis of bleeding and may be used in combination with on-demand lower cost FVIII products (as listed in *Appendix 2*) in patients without high-titer FVIII inhibitors. However, the use of Hemlibra (emicizumab-kxwh) in combination with prophylactic high-cost extended half-life (EHL) FVIII product (as listed in *Appendix 3*) is considered "not medically necessary". There is no evidence to support that the use of high-cost EHL FVIII products are safer or more effective than lower-cost FVIII products when used in combination with Hemlibra (emicizumab-kxwh).

Clinical Efficacy

Hemophilia A with FVIII Inhibitors:

Approval of Hemlibra (emicizumab-kxwh) in hemophilia A **with** FVIII inhibitors was based on two phase 3 studies. The trials were small and of fair quality overall. [1,2]

- In a randomized, open-label trial in patients with hemophilia A with high-titer FVIII inhibitors (≥5 Bethesda units), patients were randomized to receive emicizumab prophylaxis or to no treatment. Patients could receive episodic treatment with a bypassing agent for breakthrough bleeding. The annualized bleed rate (ABR) was significantly lower in patients who received treatment with Hemlibra (emicizumab-kxwh) compared to patients who received no treatment (2.9 vs. 23.3, respectively).
- A phase 3, randomized, single-arm, open-label trial evaluated Hemlibra (emicizumab-kxwh) in pediatric patients 2 to 12 years of age with hemophilia A and FVIII inhibitors. Treatment with Hemlibra (emicizumab-kxwh) demonstrated an ABR of 0.2.
- Hemlibra (emicizumab-kxwh) has not been directly compared to bypassing agents in any disease setting.

Hemophilia A WITHOUT FVIII Inhibitors:

Approval of Hemlibra (emicizumab-kxwh) in hemophilia A **without** FVIII inhibitors was based on two phase 3 studies. The trials were small and of low quality overall. [3,4]

- In HAVEN-3, emicizumab prophylactic therapy was more effective than on-demand therapy in terms of ABR. Emicizumab use resulted in an ABR (treated bleeds) of 1.5 and 1.3, compared for 38.2 for emicizumab weekly, emicizumab every 2 weeks, and on demand treatment with factor VIII product respectively. Patients could receive episodic treatment with a factor VIII product for breakthrough bleeding.
- In HAVEN-4, emicizumab dosed every 4 weeks resulted in a decrease in ABR (treated bleeds) to 2.4. The ABR prior to treatment with emicizumab was not reported. However, at baseline, 31.7% of patients in HAVEN-4 had ≥9 bleeds in the 24 weeks prior to the trial. Patients could receive episodic treatment with a factor VIII product or bypassing agent for breakthrough bleeding.
- Hemlibra (emicizumab-kxwh) has not been directly compared factor VIII replacement products in any disease setting.

Clinical Guidelines/Standard of Care Treatment

- Factor concentrate products (blood factor replacement products) are effective for the prevention and control of bleeding versus no treatment based on years of significant clinical experience, systematic reviews, and are endorsed by clinical practice guidelines. There is insufficient evidence that any factor concentrate or bypassing agent is superior to another due to a lack of comparative trial data.
- There are numerous SHL and EHL FVIII replacement products available for hemophilia A in patients without inhibitors. Whereas in patients with inhibitors, there are only a limited number of therapeutic options, including emicizumab, and FVIII inhibitor bypassing agents, such as rFVIIa (NovoSeven and SevenFact) and activated prothrombin complex concentrate (aPCC, FEIBA). [6]
- Prophylaxis is recommended as the optimal treatment modality for individuals with severe hemophilia by the National Hemophilia Foundation. The concept was conceived from the observation that moderate hemophiliacs (clotting factor level >1 IU/dL) seldom experience spontaneous bleeding and have much better preservation of joint function.[7]
- For hemophilia A patients with inhibitors on emicizumab, MASAC recommends appropriate education on management of breakthrough bleeds, caution with bypassing agent dose, and careful laboratory monitoring should occur. In addition, due to the emergence of anti-drug antibodies, careful monitoring of the continued efficacy of emicizumab is recommended.

Safety[1]

- Hemlibra (emicizumab-kxwh) has a Boxed Warning for thrombotic microangiopathy and thromboembolism when used concurrently with aPCC at >100 U/kg/day. Additional monitoring is recommended with concomitant use of the two agents.
- Hemlibra (emicizumab-kxwh) also has a warning and precaution for laboratory coagulation test interference. Intrinsic pathway clotting-laboratory tests (e.g., activated clotting time [ACT], activated partial thromboplastin time [aPTT]) should not be used to monitor Hemlibra (emicizumab-kxwh) activity.

- The most common adverse events reported include injection site reactions, headache, and arthralgia.
- There is no evidence to allow conclusion that Hemlibra (emicizumab-kxwh) is safer than FVIII products or bypassing agents.
- The recommended dose of Hemlibra (emicizumab-kxwh) is 3 mg/kg by subcutaneous injection once weekly for the first 4 weeks, followed by 1.5 mg/kg once weekly, 3mg/kg every 2 weeks, or 6mg/kg every 4 weeks. The safety and effectiveness of higher doses have not been established.

Appendix 1: Clinical Reasons Standard Half-Life (SHL) Factor Products Are Not Appropriate
Pharmacokinetic (PK) studies demonstrate an inability to maintain factor levels within the desired range with **all** recombinant SHL factor products, dosed at FDA-recommended doses.
History of bleeds despite adherence to FDA recommended doses of **all** recombinant SHL factor products.
Documented medical contraindications to **all** recombinant SHL factor products.
Inadequate venous access for prophylactic IV therapy due to comorbidities or age.
Unable to self-administer IV therapy.

Codes	Number	Description
HCPCS	J7170	Injection, emicizumab-kxwh (Hemlibra), 0.5 mg

Appendix 2: Lower-cost Factor VIII Products for Hemophilia A		
Medication	**Recombinant or Plasma-Derived**	**FDA-recommended Prophylactic Dosing**
Standard Half-Life (SHL) FVIII Products		
Advate[8]	Recombinant	Up to 40 IU/kg every other day.
Kovaltry[9]	Recombinant	>12 years old: Up to 40 IU/kg two to three times per week. <12 years old: Up to 50 IU/kg every other day.
NovoEight[10]	Recombinant	>12 years old: Up to 50 IU/kg every other day. <12 years old: Up to 60 IU/kg every other day.
Nuwiq[11]	Recombinant	>12 years old: Up to 40 IU/kg every other day. <12 years old: Up to 50 IU/kg every other day.
Xyntha[12]	Recombinant	See FDA label for specifics of maximizing dosing.
Kogenate[13]	Recombinant	Adults: Up to 25 IU/kg three times per week. Children: Up to 25 IU/kg every other day.
Recombinate[14]	Recombinant	See FDA label for specifics of maximizing dosing.
Helixate[15]	Recombinant	Adults: Up to 25 IU/kg three times per week. Children: Up to 25 IU/kg every other day.
Hemofil M[16]	Plasma	See FDA label for specifics of maximizing dosing.
Monoclate-P[17]	Plasma	See FDA label for specifics of maximizing dosing.
Alphanate[18]	Plasma	See FDA label for specifics of maximizing dosing.
Koate-DVI[19]	Plasma	See FDA label for specifics of maximizing dosing.
Humate-P[20]	Plasma	See FDA label for specifics of maximizing dosing.
Lower-cost Extended Half-Life (EHL) FVIII Products		
Afstyla [23]	Recombinant	>12 years old: Up to 50 IU/kg 2 to 3 times per week. <12 years old: Up to 50 IU/kg every other day.

Appendix 3: High- Cost Extended Half-life (EHL) Factor VIII Products for Hemophilia A		
Medication	**Recombinant or Plasma-Derived**	**FDA- recommended Prophylactic Dosing**
Adynovate[21]	Recombinant	>12 years old: Up to 50 IU/kg two times per week. <12 years old: Initially up to 55 IU/kg two times per week with a maximum of 70 IU/kg.
Eloctate[22]	Recombinant	>6 years old: Up to 65 IU/kg every 3 to 5 days. <6 years old: Up to 65 IU/kg every 3 to 5 days. More frequent or higher doses (up to 80 IU/kg) may be required.
Jivi[24]	Recombinant	>12 years old: Up to 40 IU/kg twice weekly. <12 years old: Not approved for use in this age group.
Esperoct[25]	Recombinant	>12 years old: Up to 50 IU/kg every 4 days. <12 years old: Up to 65 IU/kg twice weekly.

Cross References
Blood Factors for Hemophilia A, Extended Half-Life Products, Medication Policy Manual, Policy No. 549

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23. Afstyla [Prescribing Information]. Kankakee, IL: CSL Behring; September 2017
24. Jivi [Prescribing Information]. Whippany, NJ: Bayer; August 2018
25. Esperoct [Prescribing Information]. Plainsboro, NJ: Novo Nordisk; 2019

Revision History

Revision Date	Revision Summary
6/20/2024	• Updated COT language for operational consistency (no change to intent). • Simplified coverage criteria for "Hemophilia A without FVIII inhibitors" (removed requirement for documentation of "no inhibitors"). No change to intent. • Change step therapy requirement from "standard half-life factor products" to "lower-cost factor VIII products."
6/15/2023	No criteria changes with this annual update.
6/17/2022	No criteria changes with this annual update.
7/16/2021	No criteria changes with this annual update.
1/20/2021	• Updated COT language, no change to intent. • Made operational improvements to step therapy requirement language. • Extended auth period from 24 weeks to one year. • Simplified reauthorization requirements.
7/22/2020	Added continuation of therapy (COT) criteria. No other changes with this annual update.
10/23/2019	• Clarification of coverage criteria, for simplification and consistency of administration, including addition of a definition of "ineffectiveness to factor VIII" (no change to intent of coverage criteria). • Updated administration requirements to reflect coverage on either the pharmacy or medical benefit as dictated by group and member specific contract decisions. • Clarification of reauthorization criteria, to include documentation of efficacy and compliance with dosing regimen. • Clarification to include use of Hemlibra (emicizumab-kxwh) in combination with prophylactic doses of EHL FVIII products is "not medically necessary."
4/25/2019	No criteria changes with this annual update.
11/16/2018	Added coverage criteria for patients with hemophilia A without inhibitors, when prophylactic FVIII concentrate (blood factor replacement) therapy is ineffective.
3/19/2018	New policy (effective 5/1/18).

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Medication Policy Manual

Policy No: dru540

Topic: CGRP Monoclonal Antibodies

- Aimovig, erenumab
- Ajovy, fremanezumab
- Emgality, galcanezumab
- Vyepti, eptinezumab

Date of Origin: May 1, 2018

Committee Approval Date: March 6, 2025

Next Review Date: 2025

Effective Date: April 15, 2025

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

CGRP monoclonal antibodies are a type of medication used to prevent migraine and cluster headaches. They work by blocking calcitonin gene-related peptide (CGRP) or its receptor.

Policy/Criteria

Most contracts require pre-authorization approval of CGRP monoclonal antibodies prior to coverage.

I. Continuation of therapy (COT): CGRP monoclonal antibodies may be considered medically necessary for COT when criteria A AND B below are met.

A. One of the following (1, 2, or 3):

1. For diagnoses NOT listed in the coverage criteria below, full policy criteria below must be met for coverage.

OR

2. For diagnoses listed in the coverage criteria below, criteria a and b below must be met:

a. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

b. There is attestation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

3. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

AND

B. **For Vyepti (eptinezumab) only:** Site of care administration requirements are met [refer to Medication Policy Manual, Site of Care Review, dru408].

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): CGRP monoclonal antibodies may be considered medically necessary when attestation that criteria A AND B are met.

A. **One of the following is met (1 or 2):**

1. **Migraine headache prophylaxis** when criteria a through d below are met:

a. A diagnosis of **episodic or chronic migraine headaches**.

AND

b. Baseline headache days per month, including number of migraines and migraine frequency, severity, and characteristics.

AND

c. An adequate trial of at least one prophylactic therapy, as specified in criteria i through iii below was ineffective, not tolerated, or contraindicated:

i. Topiramate **OR** divalproex sodium (Depakote).

OR

ii. A beta blocker (such as propranolol, metoprolol, or atenolol).

OR

iii. Venlafaxine **OR** a tricyclic antidepressant (such as amitriptyline or nortriptyline).

AND

d. **For Vyepti (eptinezumab) only**, treatment with all the following (i through iii) have been ineffective, not tolerated, or are contraindicated:

i. Aimovig (erenumab).

AND

ii. Ajovy (fremanezumab).

AND

iii. Emgality (galcanezumab).

OR

2. **Episodic cluster headaches prophylaxis** for **Emgality (galcanezumab) only**, attestation that criteria a through d below are met:

a. The patient has a diagnosis of **episodic cluster headache** as confirmed by all the following (criteria i through iii):

i. The patient has had at least 5 cluster headache attacks.

AND

ii. The patient has at least two cluster periods lasting 7 to 365 days.

AND

iii. The patient's cluster periods are separated by a pain-free remission period of at least 3 months.

AND

b. Baseline cluster headache attacks per week and cluster headache frequency, severity, and characteristics.

AND

c. An evaluation has been performed to assess for rebound headaches caused by medication use [medication overuse headache (MOH)] and the patient does not suffer from rebound or MOH. Medications that may be associated with rebound headache include, but are not limited to, more than 12 doses per month of narcotics, triptans, caffeine, and NSAIDs.

AND

d. An adequate trial of at least one prophylactic therapy, as specified in criteria i through iv below, was ineffective, not tolerated, or contraindicated:

i. Verapamil.

OR

ii. Melatonin.

OR

iii. Corticosteroids [such as prednisone, methylprednisolone (Medrol Dose Pak, etc.)].

OR

iv. Lithium.

AND

B. **For Vyepti (eptinezumab) only:** Site of care administration requirements are met [refer to Medication Policy Manual, Site of Care Review, dru408].

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Aimovig (erenumab) and Emgality (galcanezumab) coverable only under the pharmacy benefit (as self-administered medications).

B. Regence Pharmacy Services considers Vyepti (eptinezumab) coverable only under the medical benefit (as a provider-administered medication).

C. Regence Pharmacy Services considers Ajovy (fremanezumab) coverable under the pharmacy benefit (as a self-administered medication) OR coverable under the medical benefit (as a provider-administered medication).

D. When pre-authorization is approved, monoclonal antibodies for migraine prevention may be authorized as follows:

1. **Initial authorization**:

a. **Aimovig (erenumab):** Up to 140 mg once monthly for six months.

b. **Ajovy (fremanezumab):** Up to 225 mg once monthly OR up to 675 mg every three months for six months.

c. **Vyepti (eptinezumab):** Up to 100 mg once every 3 months for six months.

d. **Emgality (galcanezumab):**

i. Migraine: Up to 240 mg loading dose once, followed up to 120 mg once monthly for six months.

ii. Cluster Headache: Up to 300 mg loading dose, followed up to 300 mg once monthly for six months.

2. **Continued authorization**: Continued authorization **shall** be reviewed at least annually. Attestation is required to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as headache relief or symptom improvement. This includes an improvement in functional impairment, and at least a 50% reduction in migraine frequency or cluster headache attacks, or at least a 50% reduction in severity relative to baseline migraine frequency and severity, as measured by a reduction in the need for acute therapies, additional acute care, missed school/work, or ability to perform activities of daily living (ADLs).

a. **Aimovig (erenumab):** Up to 140 mg once monthly for twelve months.

b. **Ajovy (fremanezumab):** Up to 225 mg every month for twelve months (12 doses per 12 months) OR up to 675 mg every three month for twelve months (4 doses per 12 months).

c. **Vyepti (eptinezumab):** Up to 100 mg once every 3 months for twelve months. Up to 300 mg every 3 months may be authorized in patients who have had an inadequate response to the 100 mg dose after at least six months.

d. **Emgality (galcanezumab)**:

i. Migraine: Up to 120 mg once monthly for twelve months.

ii. Cluster headache: Up to 300 mg once monthly for twelve months.

IV. Investigational uses:

A. CGRP monoclonal antibodies are considered investigational for all other indications not specified in the coverage criteria above, including chronic daily headache (CDH), tension headache, cervicogenic headache, and menstrual migraines.

B. Coadministration or combination use of any two *prophylactic* CGRP receptor antagonists (oral or injectable agents).

Position Statement

- Medications in this policy are monoclonal antibodies which target calcitonin gene-related peptide (CGRP). They are approved for the prevention of chronic and episodic migraines. Emgality (galcanezumab) is also approved for episodic cluster headaches.
- The intent of the policy is to allow coverage of CGRP monoclonal antibodies for patients with episodic or chronic migraine headaches or cluster headaches who have failed other standard of care preventative ("prophylactic") measures. Coverage of certain CGRP products is restricted to use only when treatment with preferred CGRP products have been ineffective, not tolerated, or contraindicated.
- Frequent migraine headaches may be classified as either episodic or chronic. Episodic migraine is defined as having migraine headaches for up to 14 days per month. Chronic migraine is defined as having 15 or more headache days per month for at least 3 months. [1-3]
- The starting does of Vyepti (eptinezumab) is 100 mg intravenously (IV) every 3 months, but some patients may benefit from 300 mg every 3 months. In clinical trials, patients received placebo, 100 mg, or 300 mg every three months. Both doses were superior to placebo, but the 100 mg and 300 mg doses were not compared to each other. While the 300 mg dose did appear reduce migraine days slightly more than the 100 mg dose, the differences were small and may not have been clinically meaningful. Therefore, due to similar efficacy between both doses through at least 6 months, use of the higher dose 300 mg is limited to patients who have had an inadequate response to at least two doses of Vyepti (eptinezumab) 100 mg. Additional studies are needed to determine when dose escalation is necessary and to identify if certain patients would benefit from higher doses initially.[4]
- There is no evidence directly comparing monoclonal CGRP inhibitors to oral preventative medications for migraine or cluster headaches.
- Because no CGRP monoclonal antibody migraine medication has been shown to be more effective than another, the preferred products offer members the best value. The long-term safety and durability of effect for any of these medications has not been established in the medical literature.

Use of Oral Prophylactic Therapies

- Migraines [5]:
    * A recent update (2024) to the American Headache Society's (AHS) position statement on the prevention of migraines included the addition of anti-CGRP monoclonal antibodies, oral Nurtec (rimegepant) and Qulipta (atogepant) as first line agents to be considered *along with*, and *not* a replacement for, current, well-established, first-line prophylactic treatment options such as topiramate, divalproex sodium, certain beta blockers, certain tricyclic antidepressants etc. However, given the absence of direct comparison trials between anti-CGRP agents and currently recommended first line prophylactic therapies, and somewhat limited long-term safety and efficacy evidence of anti-CGRP agents relative to other first line treatments, it is currently unknown which of the above agents, if any, is more efficacious or safer than another. Therefore, the best value

for prophylactic treatment is with agents that have established long-term efficacy and familiar safety profiles, and that are less costly.

    * Carbamazepine and a variety of select antihypertensives (candesartan, lisinopril, clonidine, guanfacine, or pindolol) are possibly effective; however, the many other prophylactic alternatives with higher-quality evidence should be used first.
    * Many other medications, including but not limited to, selective serotonin receptor inhibitors (SSRIs; e.g., fluoxetine, fluvoxamine), other SNRIs (e.g. duloxetine), other AEDs (gabapentin, lamotrigine, and oxcarbazepine), calcium channel blockers (CCBs; e.g. nicardipine, nifedipine, verapamil), and clonazepam, have been studied in migraine prophylaxis, but evidence supporting their efficacy is conflicting, inadequate, or negative (i.e., support the therapy is ineffective).

- Episodic cluster headaches[6]
    * The AHS guidelines recognize suboccipital steroid injections, lithium, verapamil, warfarin, and melatonin as possible treatment options for the prevention of episodic cluster headaches.

Summary

CLINICAL EFFICACY - MIGRAINES

- Erenumab is approved for the prevention of episodic and chronic migraine headaches based on phase 2 and 3 trials at doses of 70 or 140 mg administered as a subcutaneous injection every 4 weeks. [7-11] While erenumab demonstrated a statistically significant reduction in migraine days per month compared to placebo, the magnitude of difference is small and limited to 12 to 24 weeks of efficacy data.
- Fremanezumab is approved for the prevention of episodic and chronic migraine headaches in phase 3 trials at doses of 225 mg administered as a subcutaneous injection every four weeks or 675 mg quarterly (every 12 weeks). Fremanezumab demonstrated a statistically significant, yet marginal reduction in migraine days per month compared to placebo in 12 weeks trials.[12 13]
- Galcanezumab has been studied for the prevention of episodic migraine headaches in a phase 3 trials at doses of 120 and 240 mg administered as a subcutaneous injection every 4 weeks. Galcanezumab demonstrated a statistically significant, yet marginal reduction in migraine days per month compared to placebo in 6-month trials.[14 15]
- [16]
- Eptinezumab is approved for the preventive treatment of migraine in adults based on two phase 3 trials at doses of 100 mg and 300 mg administered intravenously every 3 months. Eptinezumab demonstrated statistically significant, yet marginal reductions in monthly migraine days compared to placebo in patients with episodic and chronic migraine.[17 18]
- The starting does of Vyepti (eptinezumab) is 100 mg intravenously (IV) every 3 months, but some patients may benefit from 300 mg every 3 months. In clinical trials, patients received placebo, 100 mg, or 300 mg every three months. Both doses were superior to placebo, but the 100 mg and 300 mg doses were not compared statistically.
    * In a trial in episodic migraine the 100 mg and 300 mg doses reduced mean migraine days by 3.9 and 4.3 days at 3 months, respectively.[17]

    * In the CM study, 100 mg and 300 mg doses reduced mean migraine days by 7.7 and 8.2 at 3 months, respectively.[19]
    * In both trials, efficacy was also similar for months 3 to 6.
- While the 300 mg dose did appear reduce migraine days slightly more than the 100 mg dose, the differences were small and may not have been clinically meaningful. Therefore, due to similar efficacy between both doses through at least 6 months, use of the higher dose 300 mg is limited to patients who have had an inadequate response to at least two doses of Vyepti (eptinezumab) 100 mg. Additional studies are needed to determine when dose escalation is necessary and to identify if certain patients would benefit from higher doses initially.[4]

CLINICAL EFFICACY – CLUSTER HEADACHES

- Galcanezumab brings uncertain value to the treatment of cluster headaches.
    * Galcanezumab has been studied for the prevention of episodic cluster headache attacks in a phase 3 trial at a dose of 300 mg administered as a subcutaneous injection at the onset of the cluster headache and once monthly thereafter until the end of the cluster period.
    * While the galcanezumab trial demonstrated a statistically significant reduction in cluster headache attacks compared to placebo at 3 weeks the treatment effect was similar to placebo at week 8. Additionally, the magnitude of difference is small, there are significant limitations in the applicability of the data, and very limited experience beyond 8 weeks.[16]

INVESTIGATIONAL USES

- There are no published clinical trials evaluating the efficacy or safety of combination use of prophylactic oral or prophylactic injectable agents with each other.
- In clinical trials involving oral prophylactic agents [Nurtec (rimegepant) or Qulipta (atogepant)], the use of injectable prophylactic CGRP agents was not allowed. Therefore, it is uncertain if combination use of prophylactic agents (oral or injectable) provides cumulative benefit over a single medication alone. There is also limited safety data on combined use of injectable and oral CGRP inhibitors with each other.

SAFETY [4 20-22]

- The long-term safety of all CGRP-targeted therapies has yet to be established in large populations. Given the mechanism of action of CGRP inhibitors, long-term safety data is needed to assess any unknown risks of long-term inhibition of CGRP and its receptor.
- In 12- to 24-week clinical trials, the most reported reactions were injection site reactions, upper respiratory tract infections, nausea, nasopharyngitis, constipation, muscle spasms, and migraine.

DOSING CONSIDERATIONS

- For migraine prophylaxis:
    * Erenumab is dosed as 70 mg subcutaneous injection every 4 weeks. Some patients may benefit from a dosage of 140 mg once monthly.
    * Fremanezumab is dosed as 225 mg subcutaneous injection every month or consolidated to 675mg every three months.

* Eptinezumab is dosed as 100 mg intravenously every 3 months. Some patients may benefit from a dosage of 300 mg.
* Galcanezumab is dosed as 240 mg loading dose (administered as two consecutive injections of 120 mg each), followed by 120 mg every month.

- For cluster headache prophylaxis, galcanezumab is dosed as 300 mg at the onset of an attack (administered as three consecutive injections of 100 mg each), followed by 300 mg every month.

Appendix 1: International Headache Society Classification of Chronic Migraine Headache [3]

A. Headache (tension-type and/or migraine) on 15 or more days per month for at least 3 months.*

B. Occurring in a patient who has had at least 5 attacks fulfilling criteria for a migraine without an aura.

C. On 8 or more days per month for at least 3 months headache has fulfilled criteria for pain and associated symptoms of migraine without aura in either or both of criteria 1 or 2 below:

1. At least two of the following criteria a), b), c), and d) below are met:
   a) Unilateral location
   b) Pulsating quality
   c) Moderate or severe pain intensity
   d) Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)

   AND at least one of the following criteria e) or f) below are met:
   e) Nausea and/or vomiting
   f) Photophobia and phonophobia
2. Treated and relieved by triptan(s) or ergot before the expected development of the above symptoms.

D. No medication overuse and not attributed to another causative disorder.

* Characterization of frequently recurring headache generally requires a headache diary to record information on pain and associated symptoms day-by-day for at least one month. Sample diaries are available at HEADACHE-DIARY.pdf (headaches.org).

Appendix 2: International Headache Society Classification of Episodic Cluster Headache [3]

A. At least five attacks fulfilling criteria B-D

B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15-180 minutes (when untreated)

C. Either one or both of the following:

1. At least one of the following symptoms or signs, ipsilateral to the headache:
    a) conjunctival injection and/or lacrimation
    b) nasal congestion and/or rhinorrhea
    c) eyelid edema
    d) forehead and facial sweating
    e) miosis and/or ptosis
2. A sense of restlessness or agitation.

D. Occurring with a frequency between one every other day and 8 per day.

E. Not better accounted for by another diagnosis.

Episodic Cluster Headache Criteria:

A. Attacks fulfilling criteria for Cluster headache and occurring in bouts (cluster periods)

B. At least two cluster periods lasting from 7 days to 1 year (when untreated) and separated by pain-free remission periods of ≥3 months.

Cross References
BlueCross BlueShield Association Medical Policy, 5.01.05 - Label Use of Botulinum Toxin. [November 2022]
Botulinum toxin type A injection, Medication Policy Manual, Policy No. dru006
Myobloc, rimabotulinumtoxinB, Medication Policy Manual, Policy No. dru048
Self-administered CGRP antagonists and 5-HT 1f agonists, Medication Policy Manual, Policy No. dru635
Site of Care Review, Medication Policy Manual, Policy No. dru408

Codes	Number	Description
HCPCS	J3031	Injection, fremanezumab-vfrm (Ajovy), 1 mg
HCPCS	J3032	Injection, eptinezumab-jjmr (Vyepti), 1 mg

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21. Aimovig (erenumab-aooe) [prescribing information]. Thousand Oaks, CA: Amgen Inc.; December 2019.

22. Ajovy (fremanezumab-vfrm) [prescribing information]. North Wales, PA: Teva Pharmaceuticals USA, Inc.; January 2020.

Revision History

Revision Date	Revision Summary
3/6/2025	Updated requirements from documentation to attestation. Removed specialist requirement for Emgality for cluster headaches.
12/12/2024	Updated investigational uses (combination use of any prophylactic agents with each other, oral or injectable).
12/07/2023	Updated criteria for migraine prophylactic therapy: removed specialist requirement for improved access and treatment of migraines by PCPs. Note: Kept specialist requirement for episodic cluster headache prophylaxis indication only for Emgality (galcanezumab).
9/14/2023	No criteria changes with this annual review. Updating to align with changes to dru635, Self-administered CGRP antagonists and 5-HT 1f agonists.
12/9/2022	• Added updated guideline consensus statement. • No criteria changes with this update
10/15/2021	• Added Site of Care requirements for Vyepti (eptinezumab). • Removed preferred product step therapy requirements for Ajovy (fremanezumab). • Updated benefit and administration language section.
1/20/2021	Updated Continuation of Therapy (COT) language. No change to intent of policy or COT.
10/28/2020	Removed migraine criterion related to medication overuse headache (MOH).
7/22/2020	• Add Continuation of Therapy (COT) language. • Added Vyepti (eptinezumab) to policy (effective 8/15/20).
10/23/2019	Added coverage criteria for Emgality (galcanezumab) use in episodic

Revision Date	Revision Summary
	cluster headaches. Limits use of Emgality (galcanezumab) for the prevention of episodic cluster headaches in patients that are refractory or have a contraindication to low-cost preventative therapy option (effective 1/1/2020).
1/31/2019	No criteria change with this annual update.
12/17/2018	Revised step therapy criteria.
11/16/2018	Clarified intent of policy.
10/19/2018	Emgality now FDA approved. Added FDA dosing and benefit coverage.
9/21/2018	• Ajovy now FDA approved. Added FDA dosing and benefit coverage. • Clarified intent of documenting baseline migraine headache frequency and severity in the criteria. No change to intent.
8/17/2018	Added criteria for use in episodic migraine.
4/20/2018	New policy.

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Medication Policy Manual | **Policy No:** dru541

Topic: Supprelin LA, histrelin acetate implant | **Date of Origin:** November 1, 2018

Committee Approval Date: October 28, 2020 | **Next Review Date:** October 2021

Effective Date: January 1, 2021

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Histrelin implant (Supprelin LA) is a gonadotropin releasing hormone (GnRH) indicated for the treatment of children with central precocious puberty (CPP). It is available as a subcutaneous implant, which is inserted by a healthcare professional and dosed every 12 months.

Policy/Criteria

Most contracts require pre-authorization approval of histrelin implant (Supprelin LA) prior to coverage.

I. Continuation of therapy (COT): Histrelin implant (Supprelin LA) may be considered medically necessary for COT when full policy criteria below are met, including quantity limit.

Please note: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan

II. Histrelin implant (Supprelin LA) is considered not medically necessary for all indications.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers histrelin implant (Supprelin LA) to be a self-administered medication. provider-administered medication.

B. When pre-authorization is approved, histrelin acetate (Supprelin LA) may be authorized in quantities of up to one implant every 12 months.

C. Authorization may be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met and that the medication is providing clinical benefit, such as disease stability or improvement.

Position Statement

Summary

- Histrelin implant (Supprelin LA) is a GnRH product indicated for the treatment of children with central precocious puberty (CPP). [1]
- Vantas, another histrelin subcutaneous implant product dosed every 12 months, is available without pre-authorization review (as of the Effective Date of this policy). For details of other available GnRH agonists, see *Appendix 1*.
- Other GnRH products including leuprolide (Lupron Depot-Ped), nafarelin (Synarel), and triptorelin (Triptodur) are available for the treatment of CPP. These products vary by the route of administration, dosing, and duration of action (See *Appendix 1*).
- Consensus guidelines equally recommend treatment with the GnRH agonists, but do not recommend one specific option over another, including dosage form. [2]
- Other GnRH products are available that provide better value. Histrelin implant (Supprelin LA) has not been proven to be safer or more effective than other products, but may be more costly than other GnRH treatment alternatives.
- The recommended dose of histrelin acetate (Supprelin LA) is one implant every 12 months. The implant is inserted subcutaneously and provides continuous release of histrelin for 12 months.

Clinical Efficacy

- Approval of histrelin implant (Supprelin LA) in the treatment of CPP was demonstrated in two, single-arm, open label studies. In both trials, suppression of luteinizing hormone was induced in all treatment-naïve subjects and maintained in all pretreated subjects at month 1 after implantation and continued through month 12. [3,4]
- There are no clinical trials demonstrating that one GnRH is superior to another in the treatment of children with CPP, in terms of either safety or efficacy.
- Evidence-based recommendations for CPP have determined that GnRH agonists are all effective despite their differences in routes of administration, dosing, and duration of action. No one product is recommended over another; however, depot preparations are often preferred because of improved compliance. [2]

APPENDIX 1

Medication	FDA Approved Indication	Dosing	Route	Administration/ Benefit	Cost (AWP)
Histrelin acetate (Supprelin LA)	Central precocious puberty in children	One 50 mg implant every 12 months inserted SC in the inner aspect of the upper arm, delivering approximately 65 mcg histrelin per day over 12 months	SC implant	Provider/Medical	$47,000/year
Histrelin acetate (Vantas) [a]	Palliative treatment of advanced prostate cancer	One 50 mg implant for 12 months inserted SC in the inner aspect of the upper arm, delivering approximately 41 mcg histrelin per day over 12 months.	SC implant	Provider/Medical	$5,600/year
Leuprolide (Lupron Depot-Ped) [a]	Central precocious puberty in children	1-month suspension depot: 7.5 mg to 15 mg IM once every month based on weight 3-month suspension depot: 11.25 mg or 30 mg IM every 3 months	IM injection	Provider/Medical	1-month suspension depot: $24,200 to $48,400/year 3-month suspension depot: $43,900 to $48,400/year
Leuprolide (Fensolvi) *	Central precocious puberty in children	6-month suspension depot: 45 mg SC injection every 6 months	SC Injection	Provider/Medical	$54,000/year
Nafarelin (Synarel) [a]	Central precocious puberty in children	Two sprays (400 µg) into each nostril in the morning (4 sprays) and two sprays into each nostril in the evening (4 sprays), a total of 8 sprays (1600 µg) per day.	Nasal spray	Self-administered/ Retail	$122,000/year
Triptorelin (Triptodur) [a]	Central precocious puberty in children	22.5 mg IM injection once every 24 weeks	IM injection	Provider/Medical	$41,300/year

[a] Available without pre-authorization

IM: intramuscular; SC: subcutaneous

Codes	Number	Description
HCPCS	J9226	Histrelin implant (Supprelin LA)

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2. Carel, J, Eugster, E, Rogol, A. Consensus statement on the use of gonadotropin-releasing hormonee analogs in children. Pediatrics. 2009;123:e752-e62.
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Revision History

Revision Date	Revision Summary
10/28/2020	• Added continuation of therapy (COT) criteria. • Added Administration, Quantity Limitations, and Authorization Period • No other changes to criteria with this annual update.
10/23/2019	No coverage criteria changes with this annual update.
05/18/2018	New policy, effective 11/1/2018.

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Medication Policy Manual | **Policy No:** dru545

Topic: Lutathera, lutetium Lu 177 dotatate | **Date of Origin:** August 1, 2018

Committee Approval Date: June 20, 2024 | **Next Review Date:** 2025

Effective Date: September 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Lutathera (lutetium Lu 177 dotatate) is a radioactive injectable drug that is used for the treatment of specific gastroenteropancreatic neuroendocrine tumors (GEP-NETs) (somatostatin receptor-positive).

Policy/Criteria

Most contracts require pre-authorization approval of Lutathera (lutetium Lu 177 dotatate) prior to coverage.

I. Continuation of therapy (COT): Lutathera (lutetium Lu 177 dotatate) may be considered medically necessary for COT when criterion A, B, or C, AND D below is met

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

AND

D. "Administration, Quantity Limitations, and Authorization Period" below applies.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New Starts (treatment-naïve patients): Lutathera (lutetium Lu 177 dotatate) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A, B, and C below are met.

A. A diagnosis of unresectable, locally advanced, or metastatic **gastroenteropancreatic neuroendocrine tumors** (GEP-NETs) of the gastrointestinal tract and pancreas (such as foregut, midgut, and hindgut).

AND

B. Documentation confirming all criteria (1, 2, and 3) below:

1. One of the following is met (a or b):

a. Low or intermediate grade GEP-NET, with a documented Ki67 index ≤20%.

OR

b. The GEP-NET is well-differentiated

AND

2. Positive somatostatin receptor expression of NETs, as detected by somatostatin receptor-based imaging, such as documented uptake on an octreotide scan (octreotide scintigraphy).

AND

3. Progressive disease despite treatment with a somatostatin analog (octreotide or lanreotide) for at least 12 weeks duration.

AND

C. Use in combination with a long-acting somatostatin analog (either Sandostatin LAR [octreotide LAR] or Somatuline [lanreotide]).

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Lutathera (lutetium Lu 177 dotatate) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Lutathera (lutetium Lu 177 dotatate) may be authorized in quantities of 7.4 GBq (200 mCi) for a total of 4 doses per lifetime.

IV. Lutathera (lutetium Lu 177 dotatate) is considered investigational when used for all other conditions including but not limited to:

A. Bronchial NETs.

B. Thymus NETs.

Position Statement

Summary

- Lutathera (lutetium Lu 177 dotatate) is a radiolabeled somatostatin analog indicated for the treatment of somatostatin receptor-positive GEP-NETs in adults. [1]
- The intent of this policy is to limit coverage of Lutathera (lutetium Lu 177 dotatate) to patients with GEP-NETs (low or intermediate grade or well-differentiated) with positive somatostatin receptor expression who have progressive disease despite treatment with a somatostatin analog.
- GEP-NETs are tumors originating in the neuroendocrine cells of the gastrointestinal system or pancreas including those arising from the foregut (stomach and pancreas), midgut (distal small intestine and proximal colon), and hindgut (distal colon and rectum). [2]
- Lutathera (lutetium Lu 177 dotatate) is a first-in-class peptide receptor radionuclide therapy (PRRT). In PRRT, a cell-targeting peptide is combined with a radionuclide to create a radiopeptide. When administered into the bloodstream, the radiopeptide travels and binds to the neuroendocrine tumor cells, delivering a high dose of radiation to the

cancer. [2]

- The safety and efficacy of Lutathera (lutetium Lu 177 dotatate) was established in a phase 3, multicenter, open-label trial, given in combination with octreotide LAR. [3]
- There are no clinical trials that have demonstrated a superior benefit of Lutathera (lutetium Lu 177 dotatate) in combination with somatostatin analogs as first-line therapy over somatostatin analogs alone.
- Serious adverse effects associated with Lutathera (lutetium Lu 177 dotatate) include risk from radiation exposure, myelosuppression, secondary myelodysplastic syndrome, renal toxicity, hepatotoxicity, neuroendocrine hormonal crisis, embryo-fetal toxicity, and risk of infertility. [1]
- The recommended dose of Lutathera (lutetium Lu 177 dotatate) is 7.4 GBq (200 mCi) every 8 weeks for a total of 4 doses. The safety and effectiveness of higher doses have not been established. [1]
- Lutathera (lutetium Lu 177 dotatate) is administered in addition to treatment with octreotide LAR and short-acting octreotide for symptom control. Patients treated with Lutathera (lutetium Lu 177 dotatate) are also recommended to receive intravenous (IV) amino acid solutions throughout the Lutathera (lutetium Lu 177 dotatate) infusion and premedication with antiemetics.
- The National Comprehensive Cancer Network (NCCN) guideline recommends the use of Lutathera (lutetium Lu 177 dotatate) as a treatment option for locoregional advanced and/or metastatic somatostatin receptor-positive gastrointestinal tumors (category 1 for mid-gut tumors), pancreatic neuroendocrine tumors, after disease progression on octreotide or lanreotide. [4]
- Evidence to support the safety and effectiveness of Lutathera (lutetium Lu 177 dotatate) in other neuroendocrine tumors is lacking.

Clinical Efficacy

- The efficacy of Lutathera (lutetium Lu 177 dotatate) was evaluated in a phase 3, multicenter, open-label trial. [3]
    * Patients with midgut GEP-NETs who had disease progression despite treatment with octreotide were randomized to receive treatment with Lutathera (lutetium Lu 177 dotatate) every 8 weeks for four doses plus long-acting octreotide for symptom control, or to receive treatment with long-acting octreotide every 4 weeks.
    * Patients treated with Lutathera (lutetium Lu 177 dotatate) also received IV amino acid solution throughout the Lutathera infusion.
- The primary endpoint was progression-free survival (PFS), defined as the time from randomization to disease progression or death from any cause. At the time of study publication, PFS was not reached in patients receiving treatment with Lutathera (lutetium Lu 177 dotatate) plus octreotide compared to 8.4 months in patients receiving octreotide alone. [3]
- PFS has not been shown to correspond with improvement in any clinically relevant outcome such as improved overall survival, symptom control, or quality of life in patients

with GEP-NETs.

- The clinical trial for the FDA approval only included patients with Ki67 index of less than 20%. However, “well-differentiated NET" and tumor somatostatin receptor expression are considered the key eligibility criteria for response to Lutathera (lutetium Lu 177 dotatate) therapy. [4]

Guidelines

- Current guidelines by the NCCN include Lutathera (lutetium Lu 177 dotatate) as a category 2A treatment option for locoregional advanced and/or metastatic somatostatin receptor-positive gastrointestinal tumors (category 1 for progressive mid-gut tumors), or pancreatic neuroendocrine tumors after disease progression on octreotide or lanreotide. [4]

Investigational Uses

- Early phase studies evaluating Lutathera (lutetium Lu 177 dotatate) included small numbers of patients with bronchial and thymus NETs. Further trials with larger patient populations are needed to establish a clinical benefit.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the ‘medical necessity’ assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Safety [1]

- Serious adverse effects associated with Lutathera (lutetium Lu 177 dotatate) include risk from radiation exposure, myelosuppression, secondary myelodysplastic syndrome, renal toxicity, hepatotoxicity, neuroendocrine hormonal crisis, embryo-fetal toxicity, and risk of infertility.

Dosing [1]

- The recommended dose of Lutathera (lutetium Lu 177 dotatate) is 7.4 GBq (200 mCi) every 8 weeks for a total of 4 doses. There is no high-quality evidence to support more frequent or more than 4 doses per lifetime.
- Before initiating treatment, long-acting somatostatin analogs should be discontinued for at least 4 weeks and short-acting octreotide at least 24 hours prior to each Lutathera (lutetium Lu 177 dotatate) dose.
- During Lutathera (lutetium Lu 177 dotatate) treatment, long-acting octreotide is administered intramuscularly after each dose and short-acting octreotide is used for symptomatic management.
- Following treatment, long-acting octreotide is given every 4 weeks after completing Lutathera (lutetium Lu 177 dotatate) until disease progression or for up to 18 months following treatment initiation.
- Intravenous amino acid solutions are administered before Lutathera (lutetium Lu 177 dotatate) and continued after infusion. Antiemetics are recommended before the amino acid solution.

Cross References
BlueCross BlueShield Association Medical Policy, 6.01.60 - Therapeutic Radiopharmaceuticals in Oncology. [August 2023]
Pituitary Disorder Therapies, Medication Policy Manual, Policy No. 488

Codes	**Number**	**Description**
ICD-10	C7A.0	Malignant carcinoid tumors
HCPCS	A9513	Lutetium Lu 177, dotatate (Lutathera), therapeutic, 1 millicurie

References

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2. Lutathera (lutetium Lu 177 dotatate) Dossier. Introducing the first peptide receptor radionuclide therapy for neuroendocrine tumors. Milburn, NJ.: Advanced Accelerator Applications USA; January 2018.
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4. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology™. [Updated routinely]. [cited with policy updates and as necessary]. Available from: https://www.nccn.org/guidelines/category_1.

Revision History

Revision Date	Revision Summary
6/20/2024	No criteria changes with this annual review.
12/7/2023	No criteria changes with this annual review.
12/9/2022	No criteria changes with this annual update.
10/15/2021	• Updated COT language (no change to intent). • Clarified tumor characteristics for coverage ("well differentiated tumor," in addition to use of the Ki67 index).
10/28/2020	Added continuation of therapy (COT) criteria, no change to intent of policy.
10/23/2019	No criteria changes with this annual update.
6/15/2018	New policy.

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Medication Policy Manual | **Policy No:** dru547

Topic: Crysvita, burosumab-twza | **Date of Origin:** August 1, 2018

Committee Approval Date: September 19,2024 | **Next Review Date:** 2025

Effective Date: December 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Crysvita (burosumab-twza) is a medication used to treat specific bone conditions [X-linked hypophosphatemia (XLH) and tumor-induced osteomalacia (TIO)]. Crysvita (burosumab-twza) is given by subcutaneous (SC) injection.

Policy/Criteria

Most contracts require pre-authorization of Crysvita (burosumab-twza) prior to coverage.

I. Continuation of therapy (COT): Crysvita (burosumab-twza) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment naïve): Crysvita (burosumab-twza) may be considered medically necessary when there is clinical documentation (including chart notes) that criterion A or B below is met:

A. A diagnosis of **tumor-induced osteomalacia** (TIO) when the diagnosis is established by or in consultation with an endocrinologist or other specialist with experience with metabolic bone health.

OR

B. A diagnosis of **X-Linked Hypophosphatemia** (XLH) when criteria 1 through 4 below are met:

1. The diagnosis is established by or in consultation with an endocrinologist or other specialist with experience with metabolic bone health.

AND

2. The diagnosis of XLH is confirmed by:

a. Clinical documentation of genetic testing showing a mutation in the phosphate-regulating endopeptidase homolog X-linked (PHEX) gene.

OR

b. Elevated FGF23 levels AND biochemical findings consistent with XLH including all the following:

1. Hypophosphatemia.

2. Low-normal 1,25(OH)2D.

3. Elevated serum alkaline phosphatase (Alk phos).

4. Normal serum calcium.

AND

3. Documented clinical manifestations of symptomatic XLH, including, but not limited to, at least one of the following symptoms:

a. Radiographic evidence of active bone disease, including active fractures.

b. **Pediatric only:** Short stature, defined as two standard deviations (3rd percentile) or more below for height by age and gender, or declining growth rate (as documented with provided standard growth charts).

c. Skeletal pain or deformities.

d. Tooth abscesses.

AND

4. Activated vitamin D and phosphate supplements are ineffective (as defined by symptomatic XLH) after use for at least 12 months, unless the use of both are not tolerated or are contraindicated (see *Appendices 1, 2, and 3*). If unable to tolerate phosphate supplements, dose lowering attempts must be made to achieve the maximally tolerated therapeutic doses.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Crysvita (burosumab-twza) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Crysvita (burosumab-twza) may be authorized in quantities defined in *Tables 1* and *2* below.

Table 1: Tumor-Induced Osteomalacia (TIO) Authorization Quantity Limits (QL) and Review Criteria

	Initial Authorization	Continued Authorization
Pediatric QL	• Doses up to 0.4 mg/kg every two weeks (minimum of 10 mg and not to exceed 180 mg per dose). • Doses up to 2 mg/kg every two weeks (not to exceed 180 mg per dose) may be authorized if there is clinical documentation of an inadequate response to 0.4 mg/kg every two weeks. Inadequate response is defined as not achieving a normal serum phosphorus.	
	6 doses in 12 weeks	26 doses per 52 weeks
Adult QL	• Doses up to 0.5 mg/kg every four weeks (minimum of 10 mg and not to exceed 180 mg per dose). • Doses up to 2 mg/kg every four weeks (not to exceed 180 mg per dose) may be authorized if there is clinical documentation of an inadequate response to 0.5 mg/kg every four weeks. Inadequate response is defined as not achieving a normal serum phosphorus.	
	3 doses in 12 weeks	13 doses per 52 weeks
Reauthorization Review Criteria	**Initial Authorization: Shall** be reviewed at 12 weeks. Ongoing coverage of Crysvita (burosumab-twza) requires clinical documentation, including chart notes, that there is normalization of serum phosphorus (within laboratory's normal range, or see *Appendix 1*). If there are persistently low serum phosphorus levels after 12 weeks, no further Crysvita (burosumab-twza) will be authorized.	**Continued Authorization: Shall** be reviewed at least annually. Ongoing coverage of Crysvita (burosumab-twza) requires clinical documentation, including chart notes, that there is ongoing disease improvement defined by 1 and 2 below: **1.** Normalization of serum phosphorus (within laboratory's normal range, or see *Appendix 1*). **AND** **2.** At least one of the following: **a.** Improvement of skeletal deformities. **b.** Improvement in growth velocity. **c.** Radiographic evidence of reduced bone disease activity and/or epiphyseal healing. **d.** Reduction in tooth abscesses. **e.** Reduction in bone pain (as documented by a validated pain scale, functional improvement in ADLs, and a reduction in the use of pain medication).

Table 2: X-Linked Hypophosphatemia (XLH) Authorization Quantity Limits (QL) and Review Criteria

	Initial Authorization	Continued Authorization
Pediatric QL	• Doses up to 0.8 mg/kg every two weeks (minimum of 10 mg and not to exceed 90 mg per dose). • Doses up to 2 mg/kg every two weeks (not to exceed 90 mg per dose) may be authorized if there is clinical documentation of an inadequate response to 0.8 mg/kg every two weeks. Inadequate response is defined as not achieving a normal serum phosphorus.	
	6 doses in 12 weeks	26 doses per 52 weeks
Adult QL	Doses up to 1 mg/kg every 4 weeks (minimum of 10 mg and not to exceed 90 mg per dose).	
	3 doses in 12 weeks	13 doses per 52 weeks
Reauthorization Review Criteria	**Initial Authorization: Shall** be reviewed at 12 weeks. Ongoing coverage of Crysvita (burosumab-twza) requires clinical documentation, including chart notes, that there is normalization of serum phosphorus (within laboratory's normal range, or see *Appendix 1*). If there are persistently low serum phosphorus levels after 12 weeks, no further Crysvita (burosumab-twza) will be authorized.	**Continued Authorization: Shall** be reviewed at least annually. Ongoing coverage of Crysvita (burosumab-twza) requires clinical documentation, including chart notes, that and there is ongoing disease improvement defined by 1 and 2 below: **1.** Normalization of serum phosphorus (within laboratory's normal range, or see *Appendix 1*). **AND** **2.** At least one of the following: **a.** Improvement of skeletal deformities. **b.** Improvement in growth velocity. **c.** Radiographic evidence of reduced bone disease activity and/or epiphyseal healing. **d.** Reduction in tooth abscesses. **e.** Reduction in bone pain (as documented by a validated pain scale, functional improvement in ADLs, and a reduction in the use of pain medication).

IV. Crysvita (burosumab-twza) is considered investigational when used for all other conditions.

Position Statement

Summary

- Crysvita (burosumab-twza) is a recombinant human IgG1 monoclonal antibody used for the treatment of patients with X-linked hypophosphatemia (XLH) and tumor-induced osteomalacia (TIO).
- Intent of this policy is to allow for coverage of Crysvita (burosumab-twza) for confirmed diagnoses of TIO, as well as symptomatic XLH (when standard of care step therapy is ineffective), for up to the doses shown to be safe and effective in clinical trials, as detailed in the coverage criteria.

XLH

- XLH is a hereditary phosphate wasting condition, caused by inactivating mutations in the phosphate-regulating endopeptidase homolog X-linked (PHEX) gene. This leads to an increase in fibroblast growth factor 23 (FGF23 levels), which then causes renal wasting and decreased intestinal absorption of phosphate.
- The diagnosis is confirmed with genetic testing for the PHEX mutation. Hypophosphatemia, low-normal 1,25(OH)2D, elevated serum alkaline phosphatase (in children), and normal serum calcium are common biochemical features of XLH.
- Historically, the standard of care for XLH is treatment with activated vitamin D and phosphate supplements (conventional therapy) when pharmacologic treatment is warranted. In children, height velocity commonly improves during the initial year of conventional therapy. Crysvita (burosumab-twza) is the only medication that treats the underlying cause of XLH, elevated FGF23 levels. [1]
- XLH is a variable disease. For patients with mild disease and an absence of symptoms, the risk of adverse events from treatment does not outweigh the potential benefit. Asymptomatic and mildly symptomatic adults are often not treated with activated vitamin D or phosphate supplements, as these patients are unlikely to receive benefit from treatment. Children are started on therapy as soon as the diagnosis of XLH is confirmed.
- The safety and efficacy of Crysvita (burosumab-twza) was established based on 4 clinical trials in patients with symptomatic XLH, despite adequate trials of activated vitamin D and phosphate supplements. There is currently no data on the safety and efficacy of burosumab-twza in XLH patients that are naïve to conventional therapy with activated vitamin D and phosphate supplements.
- There is insufficient evidence to establish that Crysvita (burosumab-twza) is more effective than vitamin D and phosphate supplements at this time. In addition, no published studies have demonstrated superiority of Crysvita (burosumab-twza) as compared to activated vitamin D and phosphate supplementation in the treatment of XLH in adult patients (closed epiphyseal plate).

- Clinical trials demonstrated that Crysvita (burosumab-twza) improves serum phosphorus levels during treatment, but did not demonstrate any clinically relevant outcomes over conventional therapy. Thus, patients with serum phosphorus within the normal range may not see any additional benefit and would see an increased risk of developing adverse events due to hyperphosphatemia.
- In patients without a normalization of serum phosphorus after 12 weeks of Crysvita (burosumab-twza) treatment, continued use of Crysvita (burosumab-twza) is considered not medically necessary.
- Crysvita (burosumab-twza) may be covered in the doses shown to be safe and effective in XLH trials (up to 90 mg subcutaneously every two to four weeks depending on age). Doses higher than 90 mg per injection have not been adequately studied in XLH.

TIO

- TIO is a rare condition caused by small tumors that produce high levels of FGF23. This results in phosphate wasting and impaired vitamin D synthesis.
- Symptoms of TIO include osteomalacia, bone fractures, bone pain, and reduced mobility.
- Crysvita (burosumab-twza) may be covered in the doses shown to be safe and effective in TIO trials (up to 180 mg subcutaneously every two to four weeks depending on age). Doses higher than 180 mg per injection have not been adequately studied in TIO.
- Although Crysvita (burosumab-twza) is FDA-approved in the adult setting up to every 2 weeks, clinical trials only evaluated every 4-week dosing. Therefore, more frequent dosing than every 4 weeks is considered not medically necessary for adult TIO patients.
- It is not recommended that Crysvita (burosumab-twza) be administered concomitantly with activated vitamin D and phosphate supplements, due to the potential for hyperphosphatemia.

Clinical Efficacy

X-linked Hypophosphatemia

- The safety and efficacy of burosumab-twza in XLH was established based on four trials, one adult trial and three pediatric trials. Patients were not allowed to be on activated vitamin D or phosphate supplements during the published adult or pediatric trials, but greater than 92% of children receiving burosumab-twza had received prior activated vitamin D and phosphate therapy.
    * One adult phase 3, randomized, placebo-controlled trial found a significant difference in proportion of adult XLH patients achieving a serum phosphorus level ≥LLN in the burosumab-twza treated group (94.1%) vs placebo (7.6%) ($p<0.0001$) at 24 weeks. [2]
        - The improvement in the WOMAC stiffness scores at week 24 was also better in the burosumab-twza group versus placebo ($p<0.01$).
            - The reliability, validity and responsiveness of the WOMAC stiffness subscale has very limited data associated with its use.
        - There was no statistically significant improvement in pain or WOMAC physical function scores between the burosumab-twza and placebo groups at 24 weeks. Data after week 24 was unblinded and has not been published in any peer reviewed journal.

- An exploratory endpoint of fracture healing at 24 weeks showed a higher percentage of patients had fractures heal (43.1% and 7.7%) in the burosumab-twza versus placebo groups, respectively. After week 24, the placebo arm began receiving burosumab-twza. At week 48, fracture healing improved to 63.1% and 35.2%, in the burosumab-twza and placebo-burosumab-twza arm, respectively. [3]
- Serum phosphorus level is a surrogate endpoint that does not correlate to an improvement of clinical outcomes. In practice, response to therapy is determined by symptomatic responses, such as a decrease in bone pain, reductions in fractures, and an improvement of osteomalacia.

* One phase 3, open label, active-controlled trial (n=61) in pediatric patients with XLH (age 1-12) found a greater improvement in the Radiographic Global Impression of Change (RGI-C) in the burosumab-twza-treated group compared to the conventional therapy group. Both burosumab-twza and conventional therapy resulted in an improvement in RGI-C, however, burosumab-twza had a greater improvement (+1.9 vs +0.8) at week 40. The long-term clinical relevance and benefit of burosumab-twza versus conventional therapy is unknown at this time. [4]
* One phase 2, open label, dose-finding trial in pediatric patients with XLH (age 5-12) found an improvement in Rickets Severity Score (RSS) and RGI-C score with burosumab-twza every two weeks (at week 40). [5]
* One phase 2, open label, single arm trial in pediatric patients (age 1-4) found an improvement in serum phosphorus at week 40. [6]

<u>Tumor-induced Osteomalacia</u> [7]

- The safety and efficacy of burosumab-twza in TIO is based on the results of an ongoing, single arm, open-label, phase 2 trial (n=14). Burosumab-twza was dosed up to 2mg/kg every 4 weeks. More frequent dosing was not studied.
  * An improvement in the surrogate endpoints of serum phosphorus and other measures of osteomalacia (osteoid thickness, mineralization lag time) were improved at week 144 compared to baseline.
  * In addition, there was an improvement in reported pain scores and fracture healing at week 144, compared to baseline.

Clinical Guidelines/Standard of Care Treatment [1 8]

- Evidence-based XLH guidelines were published in 2019 and recommend the following:

  <u>Pediatric XLH</u>
  * Treat children with XLH with conventional therapy (activated vitamin D and phosphate supplementation) as soon as the diagnosis of XLH is established.
  * Most pediatric patients are treated with activated vitamin D and phosphate supplements from diagnosis until the epiphyseal plate has fused, and growth stops.
  * If available, consider burosumab-twza treatment in children with XLH ≥1 year and in adolescents with growing skeletons in the following situations: radiographic evidence of overt bone disease and disease that is refractory to conventional therapy; or complications related to conventional therapy; or

patient's inability to adhere to conventional therapy, presuming that adequate monitoring is feasible.

* Treatment goals in the pediatric population include improvement in height velocity and overall growth, correction of rickets, improvement of radiographic abnormalities, and healing of skeletal deformities.

Adult XLH

* Unlike in the pediatric population, use of activated vitamin D and phosphates supplements in the adult population is not always required. Use of these agents is associated with high burden and potentially toxic side effects. Therefore, many adults do not receive treatment for their XLH after the epiphyseal plate has fused
* Treat symptomatic adults with XLH with conventional therapy (activated vitamin D and phosphate supplementation).
* If available, consider burosumab-twza treatment in adults with XLH (XLH) with the following features: persistent bone or joint pain due to XLH, osteomalacia that limits daily activities, pseudofractures or osteomalacia-related fractures, and an insufficient response to conventional therapy.
* Treatment goals for adults include a reduction in bone pain, improvement of osteomalacia, and improvement in fracture healing or surgical recovery time.

Safety

- Several cases of hyperphosphatemia occurred in the phase 3 adult XLH trial, and subsequently required dose reduction.
- The Crysvita (burosumab-twza) prescribing information contains warnings about the risk of hypersensitivity, injection site reactions, hyperphosphatemia and nephrocalcinosis. [9]
- The most common side effects observed in patients receiving Crysvita (burosumab-twza) in clinical trials include: headache, injection site reactions, vomiting, pyrexia, pain in extremity, hyperphosphatemia, decreased vitamin D levels, tooth abscess, muscle spasms, dizziness, constipation and rash.

Dosing and administration

- Crysvita (burosumab-twza) is administered as a subcutaneous injection at doses up to every 14 days or every 28 days in the pediatric and adult XLH settings, respectively. The maximum doses are 90mg for XLH and 180 mg in TIO. The safety and efficacy of Crysvita (burosumab-twza) at higher doses or a greater frequency has not been adequately evaluated.

Appendix 1: Serum Phosphorus Levels by Age (years) [10]	
Male 1-4: 4.3-5.4mg/dL	Female 1-7: 4.3-5.4mg/dL
Male 5-13 3.7-5.4mg/dL	Female 8-13: 4.0-5.2mg/dL
Male 14-15: 3.5-5.3mg/dL	Female 14-15: 3.5-4.9mg/dL
Male 16-17: 3.1-4.7mg/dL	Female 16-17: 3.1-4.7mg/dL
Male ≥18: 2.5-4.5mg/dL	Female ≥18: 2.5-4.5mg/dL

Appendix 2: FDA-Approved Phosphate Supplements	
Initial recommended range of elemental phosphorus doses: 20-40mg/kg/day in 3-5 divided doses [1]	
Phospha 250 Neutral Tablet	K-Phos Tablet
K-Phos Neutral Tablet	Phospho-Trin 250 Neutral Tablet
Virt-Phos 250 Neutral Tablet	AV-Phos 250 Neutral
Potassium Phosphate	Sodium Phosphate

Appendix 3: FDA-Approved Activated Vitamin D	
Initial recommended range of calcitriol doses: 20 to 30 ng/kg/day in 2 to 3 divided doses. [1]	
Calcitriol	Paricalcitol
Rocaltrol	Zemplar

Codes	Number	Description
HCPCS	J0584	Injection, burosumab-twza (Crysvita) 1 mg

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Revision History

Revision Date	Revision Summary
9/19/2024	No criteria changes with this annual review.
9/14/2023	No criteria changes with this annual review.
12/9/2022	Removed from site of care (SOC) program (effective 1/15/2023).
6/17/2022	No criteria updates with this annual review.
7/16/2021	No criteria updates with this annual review.
7/22/2020	• Added continuation of therapy (COT) criteria. • Added coverage criteria for symptomatic adult XLH patients (closed epiphyseal plate) based on evolving evidence. • Added coverage criteria for tumor-induced osteomalacia (TIO), a new FDA approved indication.
7/24/2019	The covered Quantity Limitations (QL) in Section II were clarified to state "pediatric authorization." Addition of criterion to re-auth language to cover reduction in bone pain. Added to SOC program (effective 11/1/2018).
7/20/2018	New policy, effective 8/1/2018.

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Medication Policy Manual | **Policy No:** dru548

Topic: Non-preferred testosterone replacement therapy products | **Date of Origin:** September 1, 2018

Committee Approval Date: September 19, 2024 | **Next Review Date:** 2025

Effective Date: December 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Testosterone replacement therapy (TRT) products are used in the treatment of hypogonadism (testosterone deficiency), as well as gender dysphoria, delayed puberty, and metastatic breast cancer. The effectiveness of TRT is monitored by assessing serum testosterone levels, as well as improvement in symptoms, such as mood, fatigue, bone mineral density, and well-being.

Please note the following:

Not subject to pre-authorization (PA): generic testosterone injection (cypionate or enanthate),generic testosterone 1.62% gel pump bottle, and Testopel (testosterone implant pellet).

Subject to PA and included in the Compounded Medications policy (dru135): Any compounded testosterone product (such as non-FDA approved creams, gels, and implants).

Policy/Criteria

Most contracts require pre-authorization approval of non-preferred testosterone replacement therapy (TRT) products as listed in *Table 2*, prior to coverage.

I. Continuation of therapy (COT): Non-preferred testosterone replacement therapy (TRT) products (as listed in Table 2) may be considered medically necessary for COT when criterion A below is met.

A. For all non-preferred testosterone replacement therapy products (as listed in *Table 2*), criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. One of the following applies:

a. Diagnosis of gender dysphoria, delayed puberty, or metastatic breast cancer.

OR

b. Diagnosis of hypogonadism and at least one lower cost preferred TRT product (see *Appendix 1*) has been ineffective, not tolerated or is contraindicated.

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Non-preferred testosterone replacement therapy (TRT) products (as listed in *Table 2*) may be considered medically necessary when criteria in *Table 1* below is met:

Table 1: New to therapy (treatment-naïve) members:

Diagnosis	Criteria Requirements
Gender dysphoria or Hypogonadism	Treatment with **at least two** lower cost preferred TRT products (including one generic injectable TRT; see *Appendix 1*) has been ineffective, not tolerated or is contraindicated.
Metastatic breast cancer or Delayed puberty	Treatment with injectable testosterone cypionate (generic) or testosterone enanthate (generic) has been ineffective, contraindicated, or not tolerated.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers oral, nasal, topical, transdermal testosterone replacement therapy (TRT) products, and Xyosted coverable only under the pharmacy benefit (as self-administered medications).

B. Pharmacy Services considers Aveed coverable only under the medical benefit (as a provider-administered medication).

C. When pre-authorization is approved, TRT products will be authorized as follows in *Table 2*.

D. Quantities above the listed quantity limits are considered not medically necessary.

E. Authorization **may** be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

Table 2: Non-Preferred Testosterone Replacement Therapy (TRT) Products

TRT Products	Quantity Level Limitation (per month, unless noted)
Transdermal	
Testosterone gel*, solution (generics, AndroGel, Fortesta, Testim, Vogelxo)	60 packets/tubes or 2 pump bottles
Brand Androderm testosterone transdermal patch	2-mg/24 hour: 60 patches 4-mg/24 hour: 30 patches
Oral/Buccal	
Jatenzo, Kyzatrex, Tlando (testosterone undecanoate)	120 capsules
Methyltestosterone (generics, Methitest)	150 tablets/capsules
Nasal gel	
Natesto metered-dose pump bottle (testosterone nasal gel)	3 pump bottles (60 actuations per bottle)
Injection	
Xyosted (testosterone enanthate)	Up to 4 injections per 28 days (50 mg, 75 mg, or 100 mg per injection)
Aveed (testosterone undecanoate)	750 mg at initiation, 4 weeks, and every 10 weeks thereafter

* Generic testosterone 1.62% gel bottle pump does not require pre-authorization.

IV. TRT products are considered investigational when used for all other conditions, including but not limited to:

A. In women when used for post-menopausal symptoms, including but not limited to, infertility, sexual dysfunction, cognitive dysfunction, metabolic dysfunction, bone health or general well-being.

Position Statement

- Testosterone replacement therapy (TRT) is commonly used for treatment of documented primary (testicular) or secondary (hypothalamic) hypogonadism in men, delayed puberty in males, or as part of gender dysphoria therapy. All products are considered effective for increasing serum testosterone levels.
- There is no evidence demonstrating that any one TRT product is safer or more effective than the least costly generic injectable TRT options. There are no studies that directly compare the clinical effects of different TRT products.
- The intent of this policy is to encourage the use of best value (lower cost) TRT products.

Cost

- While branded TRT products are comparable in price, generic testosterone cypionate and generic testosterone enanthate offer members the best value and they are available at preferred copayments.
- Due to the availability of many testosterone formulations, quantities above the quantity limits listed above in *Table 2* are considered not medically necessary. The quantity limits listed correspond with the manufacturer's prescribing information for each medication. There is a lack of literature showing improved health outcomes and safety when the maximum dosing is exceeded.

Clinical Efficacy

- No single testosterone replacement therapy (TRT) product has been proven in reliable clinical studies to be more effective than another TRT product.
- All TRT products appear to be similarly effective based on pharmacokinetic data. There is pharmacokinetic evidence that all topical testosterone products replete testosterone levels in men with hypogonadism. [9]
- There are no trials comparing any branded TRT formulation, therefore there is no evidence that one branded TRT product is superior to another.
- Long-term health outcomes of TRT, such as decreased incidence of fracture or cardiovascular risk, are uncertain. [8,10]
- Clinical guidelines recognize TRT as standard of care and effective for treatment of hypogonadism in men. All products are considered effective in raising testosterone levels. Choice of TRT product is based on pharmacokinetics, patient preference, and cost. However, oral TRT is not recommended due to poor absorption and liver toxicity. [1]
- The efficacy of TRT has not been established in men with age-related hypogonadism.
- There are no valid, reliable, clinically relevant endpoints for studies assessing the effect of testosterone on desire, frequency of sexual activity, erectile function, mood, energy, cognitive dysfunction, metabolic dysfunction, overall quality of life, body composition (lean and fat body mass), and bone mineral density in men with age-related hypogonadism.

Safety

- Overall, testosterone topical replacement (TRT) is well tolerated. Common adverse effects (≥ 3%) include acne, gynecomastia, oral irritation (buccal formulation), headache, and enlarged prostate. The most reported adverse event with topical TRT is application site reactions. However, testosterone transdermal patch (Androderm) is associated with a significantly higher rate of skin reactions, including blistering of the skin. [7,9]

- TRT may be associated with increased risk of adverse cardiovascular outcomes (increased mortality, myocardial infarction, and stroke). Although findings in several large observational studies and meta-analyses are inconsistent, the FDA's Bone, Reproductive and Urologic Drugs Advisory Committee concluded that there is a small signal of risk. Based on conclusions reached in the advisory committee, the FDA subsequently released a drug safety communication related to the CV risk and will require labeling changes for all prescription testosterone products. [8,10-13]
- TRT is contraindicated in men with known or suspected prostate cancer. [1]
- Testosterone undecanoate (Aveed) has boxed warnings for pulmonary oil microembolism (POME) reactions and anaphylaxis. POME reactions may be life threatening; symptoms include cough, dyspnea, throat tightening, chest pain, dizziness, and syncope. Patients who received testosterone undecanoate (Aveed) must be monitored in a healthcare setting for 30 minutes post-dose in case of serious POME reactions or anaphylaxis. [7]
- Testosterone has been subject to abuse, typically at doses higher than recommended for the approved indication and in combination with other anabolic androgenic steroids. [14]
- In March 2015, the FDA released a drug safety communication clarifying that the benefits and safety of TRT have not been established for the treatment of low testosterone levels due to aging ("age-related hypogonadism"), even if a man's symptoms seem related to low testosterone. The communication also stated that there is a possible increased cardiovascular risk associated with testosterone use. [8]
- Since the initial drug safety communication, a limitation of use has been added to the prescribing information for multiple testosterone replacement products. The updated labeling states that safety and efficacy has not been established for age-related hypogonadism (also referred to as late-onset hypogonadism).
- In 2009, the FDA issued a MedWatch safety alert of inadvertent (secondary) testosterone exposure with topical testosterone gel (Testim and AndroGel), based on eight case reports of exposure in children, age nine months to five years old. Signs of virilization (development of male secondary sexual characteristics) and bone aging were observed. Boxed warnings are now required on all topical gel and solution formulations of testosterone, as well as educational REMS programs to reduce secondary exposure. [15]

Appendix 1: Lower Cost preferred Testosterone Replacement Therapy (TRT) Products [no PA required] [1]
Topical
testosterone topical gel 1.62% pump bottle
Injectable
testosterone cypionate
testosterone enanthate
Implant
Testopel (testosterone implant pellet 75mg)

[1] Note: all the TRTs in this table are FDA-approved products. *Use of compounded TRTs (non-FDA approved formulations such as creams, gels, implants) are subject to review as a "Compounded Medication"

Cross References
BlueCross BlueShield Association Medical Policy, 5.01.23 - Testosterone Replacement Therapies [August 2023]
Compounded Medications, Medication Policy Manual, Policy No. dru135

Codes	**Number**	**Description**
HCPCS	J3145	Testosterone undecanoate (Aveed), 1 mg

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Revision History

Revision Date	Revision Summary
9/19/2024	No criteria changes with this annual review.
9/14/2023	Added Testopel to Appendix 1 as a lower-cost preferred TRT product. Generic testosterone pellets are not listed as they are not FDA-approved products.
1/9/2023	• Updated products listed in Table 2. • Updated products in Appendix 1.
9/23/2022	• Added Tlando, Kyzatrex, Vogelxo, and testosterone transdermal gel (authorized generic for Vogelxo) to policy as non-preferred TRTs. • Removed Testopel and generic implants from policy. • Removed Striant from policy (discontinued as of 5/31/2020). • Updated COT language and tables to reflect changes.
3/18/2022	Updated policy to show Xyosted (testosterone enanthate) as a pharmacy benefit drug.
10/15/2021	• Moved Aveed from NMN to coverage criteria. • Updated COT language.
10/28/2020	Added investigational uses (use in post-menopausal women, including but not limited to infertility, sexual dysfunction; cognitive dysfunction, metabolic dysfunction, bone health or general well-being).
1/22/2020	Simplified policy to step therapy only. Removed most generic products from policy. Added COT language and updated references to compounded products.
10/24/2019	• Clarified coverage for new members established on TRT therapy; clarified definition of low testosterone level. • Removed brand Axiron and brand and generic Androxy from policy – no longer marketed. • Clarified that initial lab values provided for coverage must be within the last 12 months. Updated reauth criteria to clarify that lab values provided must be within the last 12 months of treatment.
4/4/2019	Added Jatenzo to policy (effective 6/3/2019).
10/19/2018	• Simplification of the criteria for gender dysphoria (effective 12/1/2018). • Removal of AndroGel 1.62% as a preferred product due to availability of a generic (effective 12/1/2018).
10/9/2018	Add Xyosted, a new branded reformulation of testosterone enanthate.
7/20/2018	New policy, effective 9/1/2018. Policy is a combination of previous separate policies for preferred and non-preferred products.

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Medication Policy Manual

Policy No: dru549

Topic: Blood Factors for Hemophilia A, high-cost extended-half-life (EHL) products

- Adynovate, antihemophilic factor (recombinant), PEGylated
- Altuviiio, antihemophilic factor (recombinant), Fc-VWF-XTEN fusion protein-ehtl
- Eloctate, antihemophilic factor (recombinant), Fc fusion protein
- Esperoct, antihemophilic factor (recombinant), glycopegylated-exei
- Jivi, antihemophilic factor (recombinant), PEGylated

Date of Origin: January 1, 2019

Committee Approval Date: June 20, 2024

Next Review Date: 2025

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IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

High-cost extended half-life (EHL) factor VIII (EHL FVIII) blood products are used for blood factor replacement in patients with hemophilia A when standard half-life (SHL) FVIII products or lower-cost EHL products are not a treatment option. They are used “on-demand” for bleeding episodes or perioperative management of bleeding, and as routine prophylaxis to reduce frequency of bleeding episodes.

Policy/Criteria

Most contracts require pre-authorization of high-cost extended half-life (EHL) blood factor VIII (EHL FVIII) products for hemophilia A prior to coverage (as listed in Table 1).

I. Continuation of therapy (COT): High-cost extended half-life (EHL) blood factor products for hemophilia A (EHL FVIII) (as listed in Table 1) may be considered medically necessary for COT when criterion A or B **AND** C below is met.

A. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

OR

B. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

AND

C. "Administration, Quantity Limitations, and Authorization Period" below applies, as well as "Not Medically Necessary" for combination therapy and Investigational Uses".

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): High-cost extended half-life (EHL) blood factor products for hemophilia A (EHL FVIII) (as listed in Table 1) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A and B below are met:

A. A diagnosis of **hemophilia A**, established by or in consultation with a hematologist.

AND

B. Lower-cost blood factor VIII products are not a treatment option, as defined by meeting one of the following criterion (1 or 2) below:

1. Lower-cost FVIII products have been ineffective as defined by the patient continuing to have documented (e.g., bleed diary or detailed provider notes) clinically significant bleeding events (such as target joint bleeds or other end organ damage) despite adherent use of lower cost FVIII products (dose and dose frequency, as listed in *Appendix 1*).

OR

2. There is a documented objective clinical reason that all available recombinant lower-cost FVIII blood factor products are not appropriate (as listed in *Appendix 2*).

PLEASE NOTE: On-demand ("PRN") use of a short half-life factor VIII product will not meet the intent of this efficacy criteria.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers extended half-life (EHL) blood factor products for hemophilia A (EHL FVIII) coverable under the medical benefit or pharmacy benefit. Determination of coverage under the pharmacy or medical benefit is based on group-specific benefits, as defined in the group and member contract (as determined by the member contract with the health plan, regardless of self- or provider-administration).

B. Quantity Limits

1. High-cost extended half-life (EHL) blood factor products for hemophilia A (EHL FVIII) will be authorized up to FDA-recommended dose and frequency limits (*Table 1*).

2. Escalated dosing (quantities above FDA-recommended dose and frequency limits) may be covered when criteria a and b below are met:

a. There is documentation that the FDA-recommended dose is ineffective (clinically significant bleeding events such as target joint bleeds or other end-organ damage while adherent to therapy).

AND

b. Attestation that the escalated dosing is supported by a full or population-based pharmacokinetic (PK) studies.

C. Authorization Periods

1. Extended half-life (EHL) blood factor products for hemophilia A (EHL FVIII) will be authorized for up to one year.

2. Authorization shall be reviewed at least annually to confirm that the medication continues to be effective.

IV. The use of extended half-life (EHL) blood factor products for hemophilia A in combination with prophylactic Hemlibra (emicizumab-kxwh) use is considered not medically necessary.

V. The use of extended half-life (EHL) blood factor products for hemophilia A (EHL FVIII) for all other conditions not specified above is considered investigational.

Table 1. High-Cost EHL FVIII products: FDA-Recommended Dose and Frequency Limits

Product	FDA-recommended Dosing	Maximum Doses (per 28 days)
Adynovate[1]	Prophylaxis: - >12 years old: Up to 50 IU/kg two times per week. - <12 years old: Initially up to 55 IU/kg two times per week with a maximum of 70 IU/kg. On-demand: Up to 50 IU/kg every 8 to 24 hours until the bleeding is resolved. Perioperative: - Minor surgery: Up to 50 IU/kg every 24 hours for at least 1 day until bleeding is resolved. - Major surgery: Up to 60 IU/kg within one hour before the operation to achieve 100 IU/dL then every 8 to 24 hours until adequate wound healing.	Prophylaxis: - >12 years old: Up to FDA-labeled dose (+/-5%) for a total of 8 doses per 28 days. - <12 years old: Up to FDA-labeled dose (+/- 5%) for a total of 8 doses per 28 days. On-demand: Up to FDA-recommended dose (+/- 5%) for the number doses requested every 28 days. Perioperative: Up to FDA- recommended dose (+/- 5%) for the number doses requested every 28 days.
Altuviiio[2]	Prophylaxis: Up to 50 IU/kg per week every 28 days. On-demand: Up to 50 IU/kg. Additional doses every 2-3 days may be considered. Perioperative: - Minor surgery: Up to 50 IU/kg. One additional dose after 2-3 days may be considered. - Major surgery: Up to 50 IU/kg. Additional doses of up to 50 IU/kg every 2-3 days may be administered as clinically needed.	Prophylaxis: Up to 50 IU/kg per week every 28 days. On-demand: Up to FDA- recommended dose (+/- 5%) for the number doses requested every 28 days. Perioperative: Up to FDA- recommended dose (+/- 5%) for the number doses requested every 28 days.

Product	FDA-recommended Dosing	Maximum Doses (per 28 days)
Eloctate[3]	Prophylaxis: - >6 years old: Administer up to 65 IU/kg every 3 to 5 days. - <6 years old: Up to 65 IU/kg every 3 to 5 days. More frequent or higher doses (up to 80 IU/kg) may be required. On-demand: Up to 50 IU/kg every 12 to 24 hours (every 8 to 24 hours in patients <6 years old) until the bleeding is resolved. Perioperative: - Minor surgery: up to 40 IU/kg every 24 hours (every 12 to 24 hours for patients <6 years old) for at least 1 day until healing is achieved. - Major surgery: pre-operative up to 60 IU/kg followed by a repeat dose of up to 50IU/kg after 8 to 24 hours (6 to 24 hours for patients <6 years old), then every 24 hours until adequate wound healing, then continue therapy for at least another 7 days.	Prophylaxis: - >12 years old: Up to FDA-recommended dose (+/-5%) for a total of 9 doses per 28 days. - <12 years old: Up to FDA-recommended dose (+/-5%) for a total of 9 doses per 28 days. On-demand: Up to FDA- recommended dose (+/- 5%) for the number doses requested every 28 days. Perioperative: Up to FDA- recommended dose (+/- 5%) for the number doses requested every 28 days.
Jivi[4]	Prophylaxis: - >12 years old: Administer Up to 40 IU/kg twice weekly. - <12 years old: Not approved for use in this age group. On-demand: Up to 50 IU/kg every 8 to 24 hours until the bleeding is resolved. Perioperative: - Minor surgery: up to 30 IU/kg every 24 hours for at least 1 day until healing is achieved. - Major surgery: pre-operative up to 50 IU/kg every 12 to 24 hours until healing is achieved, then continue therapy for at least another 7 days.	Prophylaxis: - >12 years old: Up to FDA-recommended dose (+/-5%) for a total of 8 doses per 28 days. - <12 years old: Not approved for use in this age group. On-demand: Up to FDA- recommended dose (+/- 5%) for the number doses requested every 28 days. Perioperative: Up to FDA- recommended dose (+/- 5%) for the number doses requested every 28 days.

Product	FDA-recommended Dosing	Maximum Doses (per 28 days)
Esperoct[5]	Prophylaxis: - >12 years old: Administer Up to 50 IU/kg every 4 days. - <12 years old: Administer Up to 65 IU/kg twice weekly. On-demand: - >12 years old: Up to 50 IU/kg every 24 hours until the bleeding is resolved. - <12 years old: Up to 65 IU/kg every 24 hours until the bleeding is resolved. Perioperative: - Minor Surgery: up to 50 IU/kg (>12 years old) or up to 65 IU/kg (<12 years old) once, and then every 24 hours if necessary. - Major surgery: up to 50 IU/kg (>12 years old) or up to 65 IU/kg (<12 years old) every 24 hours for the first week, and then every 48 hours thereafter until wound healing.	Prophylaxis: - >12 years old: Up to FDA-recommended dose (+/-5%) for a total of 7 doses per 28 days. - <12 years old: Up to FDA-recommended dose (+/- 5%) for a total of 8 doses per 28 days. On-demand: - >12 years old: Up to FDA-recommended dose (+/- 5%) for the number doses requested every 28 days. - <12 years old: Up to FDA-recommended dose (+/- 5%) for the number doses requested every 28 days. Perioperative: - >12 years old: Up to FDA-recommended dose (+/- 5%) for the number doses requested every 28 days. - <12 years old: Up to FDA-recommended dose (+/- 5%) for the number doses requested every 28 days.

Position Statement

Summary

- The medications covered by this policy (as listed in Table 1) are high-cost extended half-life (EHL) blood factor VIII (FVIII) products used for the treatment of patients with hemophilia A. All are recombinant products.
- Hemophilia A is an X-linked congenital bleeding disorder caused by a deficiency of coagulation FVIII, part of the intrinsic coagulation pathway.[19]
- The intent of the policy is to allow for coverage of high-cost EHL FVIII products for patients with hemophilia A when lower-cost FVIII products [including standard half-life (SHL) products or lower-cost EHL products] are ineffective or not a treatment option, as detailed in the coverage criteria, for up to the quantities in the coverage criteria.
- In addition, the intent of the policy is to ensure ongoing use of high-cost EHL FVIII is effective for reduction of bleeding and used in doses up to the coverable amount.
- Therapy should be individualized based on age, bleeding phenotype, weight, inhibitor status, history of bleeding episodes, and availability of factor concentrates. Patients with a suboptimal response to factor concentrates should be assessed for inhibitors.[19]
- The primary goal of factor replacement therapy is to prevent and treat bleeding. A reduction in bleeding events and subsequent sequalae demonstrate the efficacy of treatment.
- Patients who continue to have spontaneous clinically significant bleeds (such as target joint bleeds or other end-organ damage) or cannot maintain optimal factor levels despite adherence to adequate (FDA-recommended) doses of standard half-life (SHL) factor products may see benefit from EHL FVIII products. However, there is no evidence that high-cost EHL FVIII products are more effective than lower-cost EHL FVIII products
- There is no evidence that high-cost EHL FVIII product prophylactic regimens are safer or more effective than lower-cost FVIII product prophylactic regimens in terms of annualized bleed rates (ABR). However, high-cost EHL FVIII product prophylactic regimens are more costly than lower-cost FVIII product prophylactic regimens (including SHL FVIII products and lower-cost EHL FVIII products).
- Recombinant factor replacement products are the recommended treatment of choice for hemophilia A patients.[20] Plasma-derived (pd) SHL FVIII products are used less frequently for long-term treatment in hemophilia A, given the availability of many recombinant SHL FVIII product options and lower-risk for infection. However, use of recombinant SHL FVIII products are considered safe and effective for management of hemophilia A and the standard of care first-line option for management. Therefore, high-cost EHL FVIII products are coverable only when recombinant SHL FVIII products are ineffective, or all are medically contraindicated. Inhibitor risk is greatest during the first 50 exposures to recombinant factor VIII products and greatly diminishes after 200 treatment days. At a minimum, inhibitor screening should be completed at baseline and yearly. Immune tolerance induction (ITI) should be started as soon as possible after a high titer FVIII inhibitors are identified (defined as greater than or equal to 5 Bethesda units. [19,21] Higher dose FVIII concentrate products can be used (SHL or EHL) with high

titer FVIII inhibitors, as well as emicizumab (Hemlibra), or bypassing agents such as rFVIIa (NovoSeven or SevenFact) or aPCC (FEIBA).

- The vast majority of published data regarding EHL FVIII products have been evaluated in previously treated patients (PTPs) with no history of inhibitory antibodies. There is currently a lack of studies that demonstrate the safety and efficacy of EHL FVIII products in previously untreated patients (PUPs). In addition, patients with a history of inhibitors have been excluded from clinical research trials of EHL FVIII products.[22]
- Pharmacokinetic (PK) dosing models can be used to individualize and improve response to therapy. Classic ("full individual") PK studies are difficult to perform due to the high number of blood samples required. Population-based PK models use data from manufacturers and hemophilia treatment centers, are easy to perform, and useful to determine FVIII product dose and require much fewer samples than classic PK studies.[23] PK studies are required at the first (initial) reauthorization period, to assess for over- or under-dosing of EHL FVIII product.

Clinical Efficacy

Hemophilia A

- The safety and efficacy of EHL FVIII products (Adynovate, Eloctate, Afstyla, Jivi, Esperoct, and Altuviiio) in hemophilia A were established based on one to two open-label, non-randomized trials in each. All were effective for reduction in annualized bleeding rate (ABR) when used prophylactically versus on-demand treatment.
- At this time, there is insufficient evidence to establish high-cost EHL FVIII products have a lower risk of inhibitor development as compared to other treatment options, such as lower-cost EHL FVIII products or SHL FVIII products. Eloctate was evaluated in clinical trials for inhibitor development. No patients developed inhibitors during either trial. However, there are cases of inhibitor formation, including in previously untreated patients, in clinical practice.
- All FVIII products (SHL and EHL) are effective for achieving hemostasis based on significant clinical experience. There are no head-to-head trials of high-cost EHL FVIII products versus SHL FVIII products or lower-cost EHL FVIII products to establish superior efficacy or safety.
- Both SHL and EHL factor VIII products are given via IV infusion. For patients unable to self-administer factor VIII, SHL FVIII may be given in the clinic setting or via home infusion services.
- In patients requiring surgery/invasive procedures, factor VIII repletion may be indicated peri-operatively. However, there is no evidence that high-cost EHL is superior to lower-cost EHL FVIII or SHL FVIII options for use in this setting.

Clinical Guidelines/Standard of Care Treatment

- Factor replacement products are effective for the prevention and control of bleeding versus no treatment based on years of significant clinical experience, systematic reviews, and are endorsed by clinical practice guidelines.

- A definitive diagnosis of hemophilia A depends on an assay that demonstrates a deficiency in Factor VIII levels. [19]
    * Mild Hemophilia A: 5-40 IU/dL
    * Moderate Hemophilia A: 1-5 IU/dL
    * Severe Hemophilia A: <1 IU/dL
- Prophylaxis is recommended as the optimal treatment modality for individuals with severe hemophilia by the National Hemophilia Foundation. The concept was conceived from the observation that moderate hemophiliacs (clotting factor level >1 IU/dL) seldom experience spontaneous bleeding and have much better preservation of joint function.[19]
- The two generalized prophylactic protocols currently in use with long-term data are the Malmö and the Utrecht protocols. These protocols should be individualized for each patient. [19]
    * Malmö protocol: 25-40 IU/kg per dose administered three times a week.
    * Utrecht protocol: 15-30 IU/kg per dose administered three times a week.
- Specific factor replacement products may recommend different dosing based on clinical trial experience.
- There is insufficient evidence that any factor product is superior to another due to a lack of comparative trial data.
- According to the Medical and Scientific Advisory Council (MASAC), the rate of inhibitors observed in PUPs in unacceptably high, and clinical trials are needed to direct clinical practice and reduce inhibitor formation. There is currently a lack of studies that demonstrate the safety and efficacy of EHL FVIII products in previously untreated patients (PUPs). Up to 30% of PUPs treated with FVIII products develop inhibitors.[24]
- Historically, patients with a history of inhibitors have been excluded from clinical research trials of EHL FVIII products.[22]
- The number of doses to reduce or manage bleeds and the dosage required varies greatly between patients. Dosage is dependent upon the level of severity, the presence of an inhibitor, prescribed regimen (on-demand, prophylaxis, perioperative), the number of bleeding episodes, individual pharmacokinetics, the products utilized, and the level of physical activity.[19]
- There is significant inter-patient pharmacokinetic variability after standard doses of FVIII. Using weight-based dosing may result in overdosing or underdosing of FVIII concentrate. The use of pharmacokinetic data facilitates individualization of FVIII dosing and may decrease the time patients are below the desired trough level (<1 IU/dL). Pharmacokinetic dosing models may lead to a reduction in treatment costs and better targeting of FVIII levels.[25]
- The pricing strategy for EHL FVIII products is based on the theory that use of EHL FVIII products reduces FVIII usage; and therefore, the cost will be similar to SHL FVIII products .[22] However, a small retrospective study of hemophilia A patients switching from SHL to EHL FVIII products showed an increase in factor usage by 33% in the 6 months immediately following the transition. This was also associated by large increase

in cost (2.36 times higher), without any proven clinical outcomes, such as a reduction in bleeding events, associated with the change.[26]

- Hemlibra (emicizumab-kxwh), a monoclonal antibody for use in patients with or without inhibitors for hemophilia A is being increasing utilized due to the ease of administration and dosing frequency.
- However, Hemlibra (emicizumab-kxwh) does not treat acute or breakthrough bleeding episodes, therefore there may still be a need for utilization of FVIII products in combination with Hemlibra (emicizumab-kxwh).
- There is insufficient evidence that utilization of EHL FVIII products for acute or breakthrough bleeding are more effective than lower cost FVIII products for use in combination with Hemlibra (emicizumab-kxwh). Thus, the lower cost FVIII products are more cost-effective and the use of EHL FVIII products in combination with Hemlibra (emicizumab-kxwh) is considered "not medically necessary."

Safety

- The most common adverse reactions reported with EHL FVIII products (Adynovate, Afstyla, Eloctate Jivi, and Esperoct) during trials included arthralgia, upper respiratory tract infection, cough, headache and injection site reactions.
- In clinical trials, use of Jivi was associated with a higher risk of hypersensitivity reactions in patients <12 years old, and therefore it is not indicated in this population.

Appendix 1: Lower-cost Factor VIII Concentrates for Hemophilia A

Product	Recombinant or Plasma-Derived	FDA-recommended Prophylactic Dosing
Standard Half-life (SHL) FVIII Products		
Advate[6]	Recombinant	Up to 40 IU/kg every other day
Kovaltry[7]	Recombinant	- >12 years old: Up to 40 IU/kg two to three times per week. - <12 years old: Up to 50 IU/kg every other day.
NovoEight[8]	Recombinant	- >12 years old: Up to 50 IU/kg every other day. - <12 years old: Up to 60 IU/kg every other day.
Nuwiq[9]	Recombinant	- >12 years old: Up to 40 IU/kg every other day. - <12 years old: Up to 50 IU/kg every other day.
Xyntha[10]	Recombinant	See FDA label for specifics of maximizing dosing.
Kogenate[11]	Recombinant	- Adults: Up to 25 IU/kg three times per week. - Children: Up to 25 IU/kg every other day.
Recombinate[12]	Recombinant	See FDA label for specifics of maximizing dosing.
Helixate[13]	Recombinant	- Adults: Up to 25 IU/kg three times per week. - Children: Up to 25 IU/kg every other day.
Hemofil M[14]	Plasma	See FDA label for specifics of maximizing dosing.
Monoclate-P[15]	Plasma	See FDA label for specifics of maximizing dosing.
Alphanate[16]	Plasma	See FDA label for specifics of maximizing dosing.
Koate-DVI[17]	Plasma	See FDA label for specifics of maximizing dosing.
Humate-P[18]	Plasma	See FDA label for specifics of maximizing dosing.
Lower-cost Extended Half-life (EHL) FVIII Products		
Afstyla [27]	Recombinant	- >12 years old: Up to 50 IU/kg 2 to 3 times per week. - <12 years old: Up to 50 IU/kg every other day.

Appendix 2: Clinical Reasons Standard Half-Life (SHL) Factor Products Are Not Appropriate
Pharmacokinetic (PK) studies demonstrate an inability to maintain factor levels within the desired range with **all** recombinant SHL factor products, dosed at FDA-recommended doses
History of bleeds despite adherence to FDA recommended doses of **all** recombinant SHL factor products
Documented medical contraindications to **all** recombinant SHL factor products
The patient is being treated for a short, defined duration (e.g. perioperative prophylaxis)

Codes	Number	Description
HCPCS	J7205	Injection, factor VIII Fc fusion protein (recombinant) (Eloctate), per IU
HCPCS	J7214	Injection, factor VIII, antihemophilic factor (recombinant) (Altuviiio), per IU
HCPCS	J7207	Injection, factor VIII, antihemophilic factor (recombinant), pegylated (Adynovate), 1 IU
HCPCS	J7208	Injection, factor VIII, antihemophilic factor (recombinant), pegylated-aucl (Jivi), 1 IU
HCPCS	J7204	Injection, factor VIII, antihemophilic factor (recombinant) glycopegylated-exei (Esperoct), per IU
HCPCS	J7199	Hemophilia clotting factor, not otherwise classified
ICD-10	D66	Hereditary Factor VIII Deficiency

Cross References
Hemlibra, emicizumab-kxwh, Medication Policy Manual, Policy No. dru539

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R*evision History*

Revision Date	Revision Summary
6/20/2024	• Updated COT language, no change to intent. • Removed requirement for 50 exposure days to lower cost FVIII products. • Added combination use of EHL FVIII products with Hemlibra (emicizumab-kxwh) as “not medically necessary”
9/14/2023	Updated Altuviiio prophylaxis dosing to "Up to 50 IU/kg per week every 28 days.” No change to intent of criteria.
6/15/2023	Effective 7/15/2023: • Removed Afstyla, a lower-cost EHL FVIII product, from policy. • Renamed policy to reflect coverage of lower-cost EHL FVIII products (e.g. Afstyla) without prior authorization. • Added Altuviiio a newly-approved high-cost EHL FVIII product, to this policy. • Added coverage of high-cost EHL FVIII products for short, defined term use (e.g. perioperative prophylaxis).
6/17/2022	No changes to coverage criteria with this annual update.
7/16/2021	No changes to coverage criteria with this annual update.

Revision Date	Revision Summary
1/20/2021	• Updated COT language, no change to intent. • Removed requirements for inhibitor evaluation. • Made operational improvements to step therapy requirement language. • Updated QL language for operational efficiency. • Extended auth period from 24 weeks to one year. • Simplified reauthorization requirements.
10/28/2020	Minor formatting fixes, no changes to policy intent.
7/22/2020	Added continuation of therapy (COT) criteria. No other changes with this annual update.
10/23/2019	Effective 1/1/2020: • Added Esperoct, a newly-approved EHL FVIII product, to this policy. • Clarification of coverage criteria, for simplification and consistency of administration, including documentation needed for FVIII inhibitor status and addition of a definition of "ineffectiveness to standard half-life factor VIII" (no change to intent of coverage criteria). • Updated administration requirements to reflect coverage on either the pharmacy or medical benefit as dictated by group and member specific contract decisions. • Clarification of reauthorization criteria, to include documentation of efficacy and compliance with dosing regimen and clarification of requirements for approval of higher factor doses products.
4/25/2019	No changes to coverage criteria with this annual update.
11/16/2018	Added of Jivi, a newly-approved EHL product, to this policy (effective 1/1/2019).
8/17/2018	New policy, effective 1/1/2019

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Medication Policy Manual **Policy No:** dru550

Topic: Blood Factors for Hemophilia B, extended-half-life (EHL) products

- Alprolix, coagulation factor IX (recombinant), Fc fusion protein
- Idelvion, coagulation factor IX (recombinant), albumin fusion protein
- Rebinyn, coagulation factor IX (recombinant), GlycoPEGylated

Date of Origin: January 1, 2019

Committee Approval Date: June 20, 2024 **Next Review Date:** 2025

Effective Date: September 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Alprolix, Idelvion, Rebinyn are extended half-life (EHL) factor IX (FIX) replacement products for hemophilia B. They are covered when standard-half-life (SHL) FIX products at the optimal dose are ineffective or not a treatment option. These products are used “on-demand” for control of bleeding episodes or for perioperative management of bleeding. In addition, Alprolix and Idelvion are indicated for routine prophylaxis to reduce the frequency of bleeding episodes.

Policy/Criteria

Most contracts require pre-authorization of extended half-life (EHL) blood factor products for hemophilia B (FIX EHL factor) prior to coverage.

I. Continuation of therapy (COT): Extended half-life (EHL) blood factor products for hemophilia B (FIX EHL factor) may be considered medically necessary for COT when criterion A or B **AND** C below is met.

A. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

OR

B. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

AND

C. "Administration, Quantity Limitations, and Authorization Period" below applies, as well as "Investigational Uses".

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Extended half-life (EHL) blood factor products for hemophilia B (FIX EHL factor) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A and B below are met:

A. A diagnosis of **hemophilia B** established by or in consultation with a hematologist.

AND

B. Standard half-life (SHL) blood factor FIX (SHL FIX) products are not a treatment option, as defined by meeting one of the following (criterion 1 or 2 below):

1. SHL FIX products have been ineffective as defined by the patient continuing to have documented (e.g. bleed diary or detailed provider notes) clinically significant bleeding events (such as target joint bleeds or other end-organ damage) despite adherent use of SHL FIX products (dose and dose frequency, as listed in *Appendix 1*).

OR

2. There is a documented objective clinical reason that **all** available SHL FIX products are not appropriate (as listed in *Appendix 2*).

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers extended half-life (EHL) blood factor products for hemophilia B (FIX EHL factor) to be either self-administered medications or provider-administered medications. Determination of coverage under the pharmacy benefit or medical benefit is based on group-specific benefits, as defined in the group and member contract.

B. Quantity Limits

1. Extended half-life (EHL) blood factor products for hemophilia B (FIX EHL factor) may be authorized up to FDA-recommended dose and frequency limits (Table 1).

2. Escalated dosing (quantities above FDA-recommended dose and frequency limits) may be covered when criteria a and b below are met:

a. There is documentation that the FDA-recommended dose is ineffective (clinically significant bleeding events such as target joint bleeds or other end-organ damage while adherent to therapy).

AND

b. Attestation that the escalated dosing is supported by a full or population-based pharmacokinetic (PK) studies.

C. Authorization Periods

1. Extended half-life (EHL) blood factor products for hemophilia B (FIX EHL factor) will be authorized for up to one year.

2. Authorization **shall** be reviewed at least annually to confirm that the medication continues to be effective.

IV. The use of extended half-life (EHL) blood factor products for hemophilia B (FIX EHL factor) for all other conditions not specified above is considered investigational.

Table 1. FDA-Recommended Dose and Frequency Limits

Product	FDA-recommended Dosing	Maximum Doses (per 28 to 30 days)
Alprolix[1]	Prophylaxis: - >12 years old: Up to 50 IU/kg once weekly or 100IU/kg once every 10 days. - <12 years old: Up to 60 IU/kg once weekly. Although more frequent or higher doses may be required based on individual response. On-demand: Up to 100 IU/kg for the first dose then again every 6 to 10 hours for one additional dose. Dosing is then every 24 hours for 3 days, then every 48 hours until the healing is achieved. Perioperative: - Minor surgery: Up to 80 IU/kg as a single infusion, then every 24 to 48 hours if needed until bleeding stops (not to exceed one additional dose per 24 hours). - Major surgery: Up to 100 IU/kg as the initial dose, then repeat dose after 6-10 hours and then every 24 hours for the first 3 days. After day 3, the dosing may be extended to every 48 hours until healing is achieved.	Prophylaxis: - >12 years old: Up to FDA-labeled dosing (+/-5%) for a total of 4 doses per 28 days, based on every 7 day dosing OR up to FDA-labeled dosing (+/-5%) for a total of 3 doses per 30 days, based on every 10 day dosing. - <12 years old: Up to FDA-labeled dosing (+/-5%) for a total of 4 doses per 28 days. On-demand: Up to FDA-labeled dosing (+/-5%) for the number of doses requested every 28 days. Perioperative: Up to FDA-labeled dosing (+/-5%) for minor or major surgery the number of doses requested every 28 days.
Idelvion[2]	Prophylaxis: - >12 years old: Up to 40 IU/kg once weekly. Patients who are well controlled on this regimen may be changed to 50-75 IU/kg every 14 days. - <12 years old: Up to 55 IU/kg body weight every 7 days. On-demand: Up to 100 IU/kg every 48-72 hours for 7-14 days until bleeding stops (not to exceed one additional dose per 48 hours). Perioperative: - Minor surgery: Up to 80 IU/kg for at least 1 day, then every 48-72 hours until healing is achieved (not to exceed one additional dose per 48 hours). - Major surgery: Up to 100 IU/kg as the initial level then every 48-72 hours for 7-14 days until healing is achieved (not to exceed one additional dose per 48 hours, up to 7 doses per 14 days).	Prophylaxis: - >12 years old: Up to FDA-labeled dosing (+/-5%) for a total of 4 doses per 28 days. - <12 years old: Up to FDA-labeled dosing (+/-5%) for a total of 4 doses per 28 days. On-demand: Up to FDA-labeled dosing (+/-5%) for the number of doses requested every 28 days. Perioperative: Up to FDA-labeled dosing (+/-5%) for minor or major surgery the number of doses requested every 28 days.

Product	FDA-recommended Dosing	Maximum Doses (per 28 to 30 days)
Rebinyn[3]	On-demand: Up to 80 IU/kg for the initial dose, after which additional doses of 40 IU/kg can be given until bleeding stops. Perioperative: - Minor surgery: Up to 40 IU/kg as a single pre-operative dose. One additional dose may be given if needed. - Major surgery: Up to 80 IU/kg pre-operatively and as clinically needed for the perioperative management of bleeding, repeated doses of 40 IU/ kg (in 1-3 day intervals) within the first week after major surgery may be administered (not to exceed one additional dose per 24 hours, up to 7 doses per 7 days).	On-demand: Up to FDA-labeled dosing (+/-5%) for the number of doses requested every 28 days. Perioperative: Up to FDA-labeled dosing (+/-5%) for the number of doses requested every 28 days.

Appendix 1: Standard Half-life Factor IX Concentrates for Hemophilia B

Recombinant	Recombinant or Plasma-Derived	FDA-recommended Prophylactic Dosing
BeneFIX[4]	Recombinant	100 IU/kg once weekly (long-term prophylaxis).
Ixinity[5]	Recombinant	40 to 70 IU/kg twice weekly.
Rixubis[6]	Recombinant	>12 years: Up to 60 IU/kg twice weekly. <12 years: Up to 80IU/kg twice weekly.
AlphaNine SD[7]	Plasma	Specific prophylactic dosing based on factor IX level for each individual per FDA label.
Mononine[9]	Plasma	Up to 30 IU/kg, the frequency of administration will vary with each patient.
Profilnine[10]	Plasma	Specific prophylactic dosing based on factor IX level for each individual per FDA label.

Appendix 2: Clinical Reasons SHL Factor Products Are Not Appropriate
Pharmacokinetic (PK) studies demonstrate an inability to maintain factor levels within the desired range with **all** recombinant SHL factor concentrates
History of bleeds despite adherence to a maximum recommended dose of **all** recombinant SHL factor concentrates
Contraindications to **all** recombinant SHL factor concentrates

Position Statement

Summary

- Alprolix, Idelvion, and Rebinyn are extended half-life (EHL) blood factor IX (FIX) products used for the treatment of patients with hemophilia B. All are recombinant products.
- Hemophilia B is an X-linked congenital bleeding disorder caused by a deficiency of coagulation FIX, part of the intrinsic coagulation pathway.[11]
- The intent of the policy is to allow for coverage of EHL FIX products for patients with hemophilia B when standard-half life (SHL) FIX products are ineffective or not a treatment option, as detailed in the coverage criteria, for up to the quantities in the coverage criteria.
- In addition, the intent of the policy is to ensure ongoing use of EHL FIX is effective for reduction of bleeding and used in doses up to the coverable amount.
- Therapy should be individualized based on age, bleeding phenotype, weight, inhibitor status, history of bleeding episodes, and availability of factor concentrates. Patients with a suboptimal response to factor concentrates should be assessed for inhibitors.[11]
- The primary goal of factor replacement therapy is to prevent and treat bleeding. A reduction in bleeding events and subsequent sequalae demonstrate the efficacy of treatment.
- Patients who continue to have spontaneous clinically significant bleeds (such as target joint bleeds or other end-organ damage) or cannot maintain optimal factor levels despite adherence to adequate (FDA-recommended) doses of Standard Half-Life (SHL) factor products may see benefit from EHL FIX products.
- There is no evidence that EHL FIX product prophylactic regimens are safer or more effective than SHL FIX product prophylactic regimens in terms of annualized bleed rates (ABR). However, EHL FIX product prophylactic regimens are more costly than SHL FIX product prophylactic regimens.
- Inhibitors are seen less frequently in Hemophilia B than in Hemophilia A, with frequency of occurrence <5%. Inhibitor risk is greatest during the first 50 exposures to recombinant factor IX and greatly diminishes after 200 treatment days.[11]
- In Hemophilia B patients who develop inhibitors, up to 50% may have a severe allergic reaction to FIX administration.
- The vast majority of published data regarding EHL FIX products have been evaluated in previously treated patients (PTPs) with no history of inhibitory antibodies. There is currently a lack of studies that demonstrate the safety and efficacy of EHL FIX products in previously untreated patients (PUPs). In addition, patients with a history of inhibitors have been excluded from clinical research trials of EHL FIX products.[12]
- Recombinant factor IX products are considered the treatment of choice for Hemophilia B.[13] Use of SHL FIX products are considered safe and effective for management of hemophilia B and the standard of care first-line option for management. Therefore, EHL FIX products are coverable only when recombinant SHL FIX products are ineffective, or all are medically contraindicated.

- Pharmacokinetic (PK) dosing models can be used to individualize therapy and improve response to therapy. Classic ("full individual") PK studies are difficult to perform due to the high number of blood samples required. Population-based PK models use data from manufacturers and hemophilia treatment centers, as easy to perform, and useful to determine FIX product dose and require much fewer samples than classic PK studies. [14] PK studies are required at the first (initial) reauthorization period, to assess for over- or under-dosing of EHL FIX product.

Clinical Efficacy[1-3]

Hemophilia B

- The safety and efficacy of Alprolix, Idelvion, and Rebinyn in hemophilia B were established based on one to four open-label, non-randomized trials in each. Alprolix and Idelvion were effective for reduction in annualized bleeding rate (ABR) when used prophylactically versus on-demand treatment. Rebinyn demonstrated efficacy in stopping or preventing bleeding in the on-demand and perioperative settings.
- At this time, there is insufficient evidence to establish EHL blood factor products have a lower risk of inhibitor development. No patients developed inhibitors during clinical trials. However, there are cases of inhibitor formation, including in previously untreated patients, in clinical practice.
- All factor IX replacement products are effective for achieving hemostasis based on significant clinical experience. There are no head-to-head trials of EHL blood factor products versus SHL blood factor products to establish superior efficacy or safety.
- Both SHL and EHL factor IX products are given via IV infusion. For patients unable to self-administer factor IX, SHL FIX may be given in the clinic setting or via home infusion services
- In patients requiring surgery/invasive procedures, factor IX repletion may be indicated in the perioperative setting. However, there is no evidence that EHL is superior to SHL factor IX options for use perioperatively.

Clinical Guidelines/Standard of Care Treatment

- Factor replacement products are effective for the prevention and control of bleeding versus no treatment based on years of significant clinical experience, systematic reviews, and are endorsed by clinical practice guidelines.
- A definitive diagnosis of hemophilia B depends on an assay that demonstrates a deficiency in Factor IX levels. [11]
    * Mild Hemophilia B: 5-40 IU/dL.
    * Moderate Hemophilia B: 1-5 IU/dL.
    * Severe Hemophilia B: <1 IU/dL.
- Prophylaxis is recommended as the optimal treatment modality for individuals with severe hemophilia by the National Hemophilia Foundation. The concept was conceived from the observation that moderate hemophiliacs (clotting factor level >1 IU/dL) seldom experience spontaneous bleeding and have much better preservation of joint function.[11]

- The two generalized prophylactic protocols currently in use with long-term data are the Malmö and the Utrecht protocols. These protocols should be individualized for each patient. [11]
    * Malmö protocol: 25-40 IU/kg per dose administered two times a week.
    * Utrecht protocol: 15-30 IU/kg per dose administered two times a week.
- Specific factor replacement products may recommend different dosing based on clinical trial experience.
- There is insufficient evidence that any factor concentrate is superior to another due to a lack of comparative trial data.
- According to the Medical and Scientific Advisory Council (MASAC), the rate of inhibitors observed in PUPs in unacceptably high, and clinical trials are needed to direct clinical practice and reduce inhibitor formation. There is currently a lack of studies that demonstrate the safety and efficacy of EHL factor products in previously untreated patients (PUPs). [15]
- Historically, patients with a history of inhibitors have been excluded from clinical research trials of EHL factor products.[12]
- Unless clinically suspected, inhibitor testing in patients with hemophilia B is not necessary after 150 EDs to a specific factor replacement product.[11]
- The number of doses to reduce or manage bleeds and the dosage required varies greatly between patients. Dosage is dependent upon the level of severity, the presence of an inhibitor, prescribed regimen (on-demand, prophylaxis, perioperative), the number of bleeding episodes, individual pharmacokinetics, the products utilized, and the level of physical activity.[11]
- There is significant inter-patient pharmacokinetic variability after standard doses of FIX and using weight-based dosing may result in overdosing or underdosing of FIX concentrate. The use of pharmacokinetic data facilitates individualization of FIX dosing and may decrease the time patients are below the desired trough level (<1 IU/dL). Pharmacokinetic dosing models may lead to a reduction in treatment costs and better targeting of FIX levels.[14]
- A small retrospective study of hemophilia B patients switching from SHL to EHL factor concentrates showed a decrease in factor usage by 18% in the 6 months immediately following the transition. Although, this was associated by large increase in cost (1.97 times higher), without any proven clinical outcomes, such as a reduction in bleeding events, associated with the change. [16]

Safety[1-3]

- The most common adverse reactions reported with EHL FIX products during trials included headache and injection site reactions.

Codes	Number	Description
HCPCS	J7201	Injection, factor ix, fc fusion protein, (recombinant) (Alprolix), per IU
HCPCS	J7202	Injection, factor ix, albumin fusion protein, (recombinant) (Idelvion), 1 IU
HCPCS	J7203	Injection, factor ix, (antihemophilic factor, recombinant), glycopegylated (Rebinyn), 1 IU
ICD-10	D67	Hereditary Factor IX Deficiency

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4. BeneFIX [prescribing information]. Philadelphia, PA: Wyeth; June 2017
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6. Rixubis [prescribing information]. Westlake Village, CA: Shire; March 2016
7. AlphaNine SD [prescribing information]. Los Angeles, CA: Grifols Biologicals; March 2017
8. Bebulin [prescribing information]. Westlake Village, CA: Shire; June 2018
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Revision History

Revision Date	Revision Summary
6/20/2024	• Updated COT language, no change to intent. • Removed requirement for 50 exposure days to SHL products.
6/15/2023	No criteria changes with this annual update
6/17/2022	No criteria changes with this annual update.
7/16/2021	No criteria changes with this annual update.
1/20/2021	• Updated COT language, no change to intent. • Removed requirements for inhibitor evaluation. • Made operational improvements to step therapy requirement language. • Updated QL language for operational efficiency. • Extended auth period from 24 weeks to one year. • Simplified reauthorization requirements.
10/28/2020	Minor formatting fixes, no changes to policy intent.
7/22/2020	Added continuation of therapy (COT) criteria. No other changes with this annual update.
10/23/2019	Effective 1/1/2020: • Clarification of coverage criteria, for simplification and consistency of administration, including documentation needed for FIX inhibitor status and addition of a definition of "ineffectiveness to standard half-life factor FIX" (no change to intent of coverage criteria). • Updated administration requirements to reflect coverage on either the pharmacy or medical benefit as dictated by group and member specific contract decisions. • Clarification of reauthorization criteria, to include documentation of efficacy and compliance with dosing regimen and clarification of requirements for approval of higher factor doses products.
4/25/2019	No criteria changes with this annual update.
8/17/2018	New policy, effective 1/1/2019

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Medication Policy Manual **Policy No:** dru551

Topic: Medications for Phenylketonuria(PKU) **Date of Origin:** October 1, 2018

- Kuvan®, sapropterin
- Palynziq®, pegvaliase-pqpz

Committee Approval Date: August 17, 2018 **Next Review Date:** August 2019

Effective Date: October 1, 2018

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Sapropterin (Kuvan) and pegvaliase (Palynziq) are medications used to decrease blood phenylalanine levels in patients with Phenylketonuria (PKU). Sapropterin (Kuvan) is orally administered and used in conjunction with a phenylalanine (Phe) restricted diet to reduce blood phenylalanine levels. Pegvaliase (Palynziq) is administered subcutaneously and coverable in patients with blood Phe levels greater than 600µmol/dL on existing management.

Policy/Criteria

I. Most contracts require pre-authorization approval of medications for Phenylketonuria prior to coverage.

A. **Sapropterin (Kuvan)** may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) showing that ALL criteria (1, 2 and 3) below are met.

1. A diagnosis of phenylketonuria (PKU) has been established by a metabolic specialist.

AND

2. Phenylalanine (Phe) levels cannot be maintained within the recommended maintenance range [120-360 µmol/dL (2 – 6 mg/dL)] with dietary intervention alone.

AND

3. Documentation of an elevated average baseline blood Phe level ≥ 360 µmol/L, prior to initiating therapy with sapropterin (Kuvan) and a current body weight.

B. **Pegvaliase (Palynziq)** may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) showing that ALL criteria (1, 2, and 3) below are met.

1. A diagnosis of phenylketonuria (PKU) has been established by a metabolic specialist.

AND

2. Documentation of an elevated average baseline blood Phe level ≥ 600 µmol/L over the last 6 months prior to starting pegvaliase (Palynziq).

AND

3. Treatment with sapropterin (Kuvan) has been ineffective, not tolerated, or is contraindicated. Ineffectiveness is defined as a decrease in blood Phe levels of less than 30% from baseline after one month of treatment.

II. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers sapropterin (Kuvan) and pegvaliase (Palynziq) to be self-administered medications.

B. **Initial Authorization:** When prior authorization is approved, medications for PKU may be initially covered in quantities as follows:

Kuvan

1. Up to 10 mg/kg/day for up to two months.

2. Up to 20 mg/kg/day for up to two months, when there is clinical documentation that **current** treatment with sapropterin (Kuvan) 10 mg/kg/day is not effective after at least 8 days of sapropterin (Kuvan) treatment, defined as less than a 30% decrease in blood Phe level from baseline (the Phe level provided in criterion I.A.3. above).

NOTE: Number of tablets (or powder packets for solution) authorized per month will be rounded to the nearest 100 mg. Doses exceeding 20 mg/kg/day are considered investigational.

Palynziq

1. Up to 20mg/day for up to six months

2. Up to 40 mg/day when there is clinical documentation that current treatment with pegvaliase (Palynziq) 20 mg/day is not effective after at least 24 weeks of pegvaliase (Palynziq) treatment, defined as less than a 20% decrease in blood Phe level from baseline (the Phe level provided in criterion I.B.1 above).

C. **Continued Authorization:** Authorization for medications for PKU shall be reviewed at least every six months. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met and that the medication is providing clinical benefit, with confirmation of ALL of the following:

Kuvan

1. The blood Phe level has decreased at least 30% from baseline (the Phe level provided in criterion I.A.3 above).

AND

2. The patient remains compliant with a phenylalanine-restricted diet, based on clinical documentation.

AND

3. The dose of sapropterin (Kuvan) does not exceed 20 mg/kg/day, based on the patient's recent weight (within the last 90 days). All doses will be rounded to the nearest 100 mg.

Palynziq

1. The blood Phe level has decreased from baseline (Phe level provided in criterion I.B.1. above)

AND

2. ***For patients on Palynziq 40mg for 16 weeks:*** The blood Phe level has decreased at least 20% from baseline (the Phe level provided in criterion I.B.1. above)

III. Medications for PKU) are considered investigational when used:

A. For any condition other than phenylketonuria, including, but not limited to autism and cirrhosis with portal hypertension.

B. In combination [concomitant use of sapropterin (Kuvan) and pegvaliase (Palynziq)].

Position Statement

- The current standard of care for patients with PKU is adherence to a Phe-restricted diet.
- Sapropterin (Kuvan) is approved for the reduction of blood phenylalanine (Phe) levels in patients with high Phe levels (hyperphenylalaninemia) due to tetrahydrobiopterin (BH4)-responsive phenylketonuria (PKU), despite dietary intervention. Sapropterin (Kuvan) is to be used in conjunction with a Phe-restricted diet.
- Pegvaliase (Palynziq) is approved to reduce blood phenylalanine (Phe) levels in adults with PKU that have blood Phe levels above 600 µmol/L on existing management. It is the first PKU drug approved that does not require the adherence of a Phe-restricted diet.
- There is no data that demonstrates that either medication for PKU is more effective than the other in the treatment of PKU.
- Untreated PKU is associated with severe mental retardation, reduced IQ scores, behavioral difficulties and other symptoms. However, there is no consensus concerning the optimal blood Phe level. In addition, the blood Phe concentration associated with optimal central nervous system outcomes is uncertain.
- Although there is evidence that sapropterin (Kuvan) and pegvaliase (Palynziq) lower blood Phe levels in patients with PKU, the long-term impact on neurological development and clinically relevant outcomes is unknown. There is no evidence to indicate that sapropterin (Kuvan) or pegvaliase (Palynziq) improve long-term patient outcomes.
- There is no evidence to indicate that sapropterin (Kuvan) or pegvaliase (Palynziq) are safe or effective when used in combination for treatment of PKU.
- In clinical trials, patients were considered responders to sapropterin (Kuvan) if blood Phe levels decreased at least 30% from baseline. A response was seen as early as eight days after initiating treatment. If blood Phe levels do not decrease after one month of treatment ("non-responders"), treatment with sapropterin (Kuvan) should be discontinued.
- In clinical trials, patients were considered responders to pegvaliase (Palynziq) if blood Phe levels decreased at least 20% from baseline. If blood Phe levels do not decrease after injecting 40mg daily for 16 weeks, treatment with pegvaliase (Palynziq) should be discontinued.
- The recommended starting dose of sapropterin (Kuvan) is 10 mg/kg/day taken once daily. For patients who do not respond, the dose can be increased to 20 mg/kg/day. The efficacy and safety of higher doses has not been established.
- The recommended dose of pegvaliase (Palynziq) is 20 mg subcutaneously once daily. For patients who do not respond after 24 weeks of therapy, the dose can be increased to 40 mg subcutaneously once daily. The efficacy and safety of higher doses has not been established.
- Sapropterin (Kuvan) has an established safety profile in the treatment of PKU. Due to the risk of anaphylaxis, pegvaliase (Palynziq) has a REMS program.

Clinical Efficacy

- Sapropterin (Kuvan) The efficacy of sapropterin (Kuvan) was established based on five clinical trials: one open-label trial with a follow-on randomized controlled trial and open-label extension trial, as well as two additional Phase 3 trials.[1-5]
    - Sapropterin (Kuvan) was dosed at 10 to 20 mg/kg/day.
    - The study duration ranged from eight days to 22 weeks.
    - The primary efficacy endpoint was the change in blood Phe concentration from baseline.
    - "Responders" were defined as patients who achieved at least a 30% decrease in blood Phe levels with sapropterin (Kuvan) treatment.
- Based on the clinical trial evidence, two high quality systematic reviews concluded treatment with sapropterin (Kuvan) decreases Phe blood levels.[6,7]
    - One systematic review found Phe levels were reduced by at least 30% in up to half of sapropterin (Kuvan) treated patients (32 to 50%). [7]
    - The other systematic review found a decrease in Phe levels versus baseline in sapropterin (Kuvan) treated patients. The average reduction in those on a Phe-restricted diet was a non-statistically significant change of -51.90 µmol/L. The average reduction in those on a relaxed or abandoned Phe-restricted diet, was a statistically significant change of -238.80 µmol/L.[6]
    - PKU treatment aims to maintain blood Phe levels within recommended ranges (120-360 µmol/L), to prevent neurologic damage; however, the blood Phe concentration associated with optimal neurodevelopmental outcome is uncertain.[6,8,9]
    - There are no studies comparing the use of sapropterin (Kuvan) to a Phe-restricted diet.
- There is insufficient data to make a conclusion regarding the impact of sapropterin (Kuvan) for improving clinically meaningful outcomes such as executive function (i.e. cognition).[6,7]
    - One small case series, sited within a systematic review, reported on intelligence quotient (IQ) and nutritional outcomes. After 1 year on sapropterin (Kuvan) 5mg/kg/day, the 11 participants discontinued use of a medical food and began a normal diet. IQ scores after 12 months on sapropterin (Kuvan) were similar to scores before treatment and development quotients were within normal limits. [7]
- There are no studies which evaluate sapropterin (Kuvan) treatment for quality-of-life outcomes.[6,7]
- There is insufficient data to make a conclusion regarding the impact of sapropterin (Kuvan) in the treatment of severe PKU.[6]
- Given the variability of genetic deficiency found with hyperphenylalaninemia, patients whose blood Phe does not decrease after 1 month despite the maximum sapropterin (Kuvan) daily dose of 20 mg/kg/day are "non-responders," and treatment with sapropterin (Kuvan) should be discontinued in these patients.[5]

Pegvaliase (Palynziq)

- The safety and efficacy of pegvaliase (Palynziq) was established based off 2 low confidence, phase 3, randomized, multicenter trials (PRISM-1, PRISM-2). They were conducted in patients with PKU and baseline blood Phe levels ≥600mol/L and showed a large reduction in blood Phe compared to baseline at all time points.[10,11]
    - Use of pegvaliase (Palynziq) was associated with a reduction in cognitive and mood assessment scores from baseline while receiving treatment.
    - Treatment with pegvaliase was not compared to the standard of care, a Phe-restricted diet, or against the only other approved PKU treatment, sapropterin (Kuvan). Thus, the magnitude of benefit compared to prior therapies is unknown.
    - There are no studies of pegvaliase (Palynziq) when used in combination with sapropterin (Kuvan).

Treatment Guidelines/Standard of Care

- To achieve metabolic control, PKU guidelines recommend a life-long Phe-restricted diet, including medical foods and low-protein products, as the standard of care for PKU. [9,12]
- The primary goal of therapy is to lower blood Phe and improve psychosocial and neurocognitive function. Any interventions, including dietary restrictions, medical foods, or pharmacotherapy that helps achieve that goal without other negative consequences, should be considered appropriate therapy. Patient response to each intervention is variable and choice of treatment should be individualized. [9]
- Two systematic reviews evaluated the overall treatment of patients with PKU. [6,7]
    - The mainstay of PKU treatment is a Phe-restricted diet, ideally continued into adult life, with regular monitoring of blood Phe levels. Patients often require dietary supplements in the form of medical foods containing low-Phe protein sources.
    - Non-compliance to the restricted diet in teenagers and adults show subtle cognitive impairments relative to controls and is associated with an increase in the rate of eczema, asthma, mental disorders, headache, hyperactivity, and hypoactivity.
    - There are no definitive studies on the effects of dietary treatment in adults, but individual case reports have documented deterioration of adult PKU patients after diet discontinuation.
    - In addition, there is a lack of information on how much improvement might be expected on Phe levels with such a diet.
    - Treatment guidelines have not been updated since the approval of pegvaliase (Palynziq)

Investigational Uses

- Sapropterin (Kuvan) did not improve hepatic venous pressure gradient in subjects with cirrhosis and portal hypertension.[13]
- Sapropterin (Kuvan) did not improve Clinical Global Impressions Improvement (CGI-I) or Severity (CGI-S) in patients with autism spectrum disorders.[14]

Safety[5,15]

Kuvan

- The most common side effects observed in clinical trials include headache, upper respiratory infection, rhinorrhea, pharyngolaryngeal pain, diarrhea, nausea and vomiting.
- Children less than 7 years of age should be started on lower doses of sapropterin (Kuvan) of 10 mg/kg/day to prevent abnormally low blood Phe levels. Doses may be titrated to 20 mg/kg/day, as needed, for blood Phe level reduction.

Pegvaliase (Palynziq)

- Adverse events in the clinical trials included injection site reactions, arthralgia, hypersensitivity reactions, headache, pruritus, nausea, abdominal pain, cough, diarrhea, and fatigue.
- Immunogenicity concerns exist, and elevations in various IgM and IgG levels were noted during the trials.
- Due to the risk of anaphylaxis, pegvaliase is only available through a restricted distribution program as part of a REMS requirement. During clinical trials, 9% of patients experienced an anaphylactic event.

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Codes	Number	Description
ICD-10	E70.0	Phenylketonuria

Revision History

Revision Date	Revision Summary
07/16/2018	New policy incorporating Kuvan policy (effective date 10/1/2018).

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Medication Policy Manual **Policy No:** dru563

Topic: Non-preferred pegfilgrastim products **Date of Origin:** July 1, 2019

- Neulasta, pegfilgrastim
- Neulasta Onpro, pegfilgrastim
- Fylnetra, pegfilgrastim-pbbk
- Nyvepria, pegfilgrastim-apgf
- Stimufend, pegfilgrastim-fpgk
- Udenyca, pegfilgrastim-cbqv

Committee Approval Date: September 23, 2022 **Next Review Date:** June 2023

Effective Date: January 1, 2023

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

All forms of pegfilgrastim are long-acting granulocyte-colony stimulating factors (G-CSF) that helps reduce the risk of infections in patients undergoing strong chemotherapy which depletes the number of white blood cells available in the body. All forms of pegfilgrastim work by stimulating the production of white blood cells which are an essential component in the body's ability to fight infections.

PLEASE NOTE: This policy and the coverage criteria below do not apply to preferred pegfilgrastim products [Fulphila (pegfilgrastim-jmdb) or Ziextenzo (pegfilgrastim-bmez)]. Preferred pegfilgrastim products do not require pre-authorization.

Policy/Criteria

Most contracts require pre-authorization approval of non-preferred pegfilgrastim products (as listed in Table 1) prior to coverage.

I. Continuation of therapy (COT): Non-preferred pegfilgrastim products (as listed in Table 1) may be considered medically necessary for COT when full policy criteria below are met, including quantity limit.

Please note: *Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Non-preferred pegfilgrastim products (as listed in Table 1) may be considered medically necessary when there is clinical documentation (including chart notes) that criterion A, B, or C below are met.

A. For **non-preferred biosimilar pegfilgrastim pre-filled syringe (PFS) products (Fylnetra, Nyvepria, Stimufend, Udenyca)**: Treatment with all preferred biosimilar pegfilgrastim PFS products have been ineffective, not tolerated, or contraindicated (as listed in Table 1).

OR

B. For **pegfilgrastim pre-filled syringe (Neulasta PFS)**: Treatment with all biosimilar pegfilgrastim PFS products (preferred AND non-preferred) have all been ineffective, not tolerated, or all are contraindicated (as listed in Table 1).

OR

C. For **pegfilgrastim pre-filled autoinjector device (Neulasta Onpro)**: Criteria 1 and 2 below are met.

1. Patient or patient's caregiver is not able to self-administer any of the pegfilgrastim PFS products (as listed in Table 1) due to significant behavioral issues, physical difficulties, and/or cognitive impairment including, but not limited to, those associated with developmental delay, down syndrome, dementia, or excessive anxiety such as severe needle phobia.

AND

2. Patient lives greater than 10 miles from the providers office, such that it is not possible to return for administration of any of the pegfilgrastim PFS products (as listed in Table 1).

Table 1. Reference and Biosimilar Pegfilgrastim Products

	Product name	Formulary status	PA required?
Pre-filled Syringe (PFS) Products			
Reference Product	Neulasta PFS (pegfilgrastim)	Non-preferred	Yes
Biosimilars	Fulphila (pegfilgrastim-jmdb)	Preferred	No
	Fylnetra (pegfilgrastim-pbbk)	Non-preferred	Yes
	Nyvepria (pegfilgrastim-apgf-bvzr)	Non-preferred	Yes
	Stimufend (pegfilgrastim-fpgk)	Non-preferred	Yes
	Udenyca (pegfilgrastim-cbqv)	Non-preferred	Yes
	Ziextenzo (pegfilgrastim-bmez)	Preferred	No
Autoinjector Device Products			
Reference Product	Neulasta Onpro (pegfilgrastim)	Non-preferred	Yes
Biosimilars	none	n/a	n/a

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers all the pegfilgrastim pre-filled syringe (PFS) products (as listed in Table 1) coverable under the pharmacy benefit (as self-administered medications) OR coverable under the medical benefit (as provider-administered medications).

B. Regence Pharmacy Services considers pegfilgrastim (Neulasta Onpro) coverable only under the medical benefit (as a provider-administered medication).

C. Authorization may be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

Position Statement [1-5]

Summary

- The intent of this policy is to promote the use of biosimilar products that are the lowest overall cost. All pegfilgrastim products are considered safe and effective options.
- The policy allows for:
  * Coverage of the non-preferred pre-filled syringe (PFS) pegfilgrastim products when the preferred PFS pegfilgrastim products are ineffective, not tolerated, or contraindicated.

* Coverage of pegfilgrastim pre-filled autoinjector device (Neulasta Onpro) when the member lives too far from their provider's office to return for administration of a pre-filled syringe (PFS) product and there is documented medical rationale that a member is unable to self-administer themselves with all the PFS pegfilgrastim product options.

- There is no evidence that any one pegfilgrastim product is safer or more effective than another. Among these products, preferred PFS pegfilgrastim products provide the best value for members.
- The FDA reaffirmed the lack of superiority of one dosage form of pegfilgrastim over others. In July 2021, the FDA issued a warning to the manufacturer of Neulasta Onpro for misleading promotional material, based on an observational study. In short, the FDA determined claims of superiority of pegfilgrastim via the on-body injector Onpro over pegfilgrastim delivered through a prefilled syringe are not supported due to limitations of the available data. "The promotional communication's misleading claims and presentations could cause healthcare providers to conclude that pegfilgrastim delivered through the Onpro on-body injector is more effective than pegfilgrastim delivered through a prefilled syringe or that it is more effective than FDA-licensed biosimilar pegfilgrastim products, which are only delivered through a prefilled syringe."
- Hospitals and health-systems have medication formularies developed independent of the health plan. The health plan is unable to cover more expensive products for the convenience of the hospital, health-system, provider, or member. Preferred biosimilar products represent the lowest cost to members and the plan; the use of more expensive products without evidence of superior efficacy or safety is not medically necessary per the member's contract.

Codes	Number	Description
HCPCS	J2506	Injection, pegfilgrastim (Neulasta, Neulasta Onpro), excludes biosimilar, 0.5 mg
HCPCS	Q5108	Injection, pegfilgrastim-jmdb, biosimilar, (Fulphila), 0.5 mg
HCPCS	Q5122	Injection, pegfilgrastim-apgf, biosimilar, (Nyvepria), 0.5 mg
HCPCS	Q5111	Injection, pegfilgrastim-cbqv, biosimilar, (Udenyca), 0.5 mg

References

1. Ziextenzo [Prescribing Information]. Princeton, NJ: Sandoz; March 2021.
2. Fulphila [Prescribing Information]. Steinhausen, Switzerland: Mylan; March 2021.
3. Neulasta [Prescribing Information]. Thousand Oaks, CA: Amgen; February 2021.
4. Udenyca [Prescribing Information]. Redwood City, CA: Coherus BioSciences, Inc; June 2021: Cohrus.
5. Nyvepria [Prescribing Information]. New York, NY: Pfizer Inc; April 2021.

Revision History

Revision Date	Revision Summary
9/23/2022	• Effective 1/1/2023, updated preferred products to Fulphila and Ziextenzo. Udenyca will be non-preferred and require PA. • Added newly approved biosimilar Stimufend (pegfilgrastim-fpgk) to policy as non-preferred.
6/17/2022	• Modified criteria wording, for operational clarity (no change to intent of the criteria with this annual update). • Addition of a product table, to delineate the preferred/non-preferred, pre-filled syringe/autoinjector, and reference product/biosimilars. • Added Fylnetra (pegfilgrastim-pbbk) to policy.
7/16/2021	No criteria changes with this annual update.
10/28/2020	Added Nyvepria (pegfilgrastim-apgf) to policy.
7/22/2020	No criteria changes with this annual update.
4/22/2020	Added COT language. Added pegfilgrastim-bmez (Ziextenzo) as a preferred pegfilgrastim product.
1/31/2019	New policy. Effective 7/1/2019.

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Medication Policy Manual | **Policy No:** dru564

Topic: Lumoxiti, moxetumomab pasudotox-tdfk | **Date of Origin:** April 1, 2019

Committee Approval Date: April 21, 2021 | **Next Review Date:** April 2022

Effective Date: July 1, 2021

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Moxetumomab pasudotox-tdfk (Lumoxiti) is an intravenously (IV) infused medication used in the treatment of patients with hairy cell leukemia (HCL) after standard front-line therapies.

Policy/Criteria

Most contracts require pre-authorization approval of moxetumomab pasudotox-tdfk (Lumoxiti) prior to coverage.

I. Continuation of therapy (COT): Moxetumomab pasudotox-tdfk (Lumoxiti) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Moxetumomab pasudotox-tdfk (Lumoxiti) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that all criteria A, B, and C below are met:

A. A diagnosis of relapsed or refractory hairy cell leukemia (HCL).

AND

B. At least two prior systemic therapies for HCL have been ineffective or not tolerated, including treatment with cladribine or pentostatin (purine nucleoside analog).

AND

C. Moxetumomab pasudotox-tdfk (Lumoxiti) will be used as monotherapy.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services does not consider moxetumomab pasudotox-tdfk (Lumoxiti) to be a self-administered medication.

B. When pre-authorization is approved, moxetumomab pasudotox-tdfk (Lumoxiti) will be authorized for up to a total of 18 infusions (six cycles) over a 12-month period, based on a dose of 0.04 mg/kg on days 1, 3, and 5 every 28-day cycle, for six cycles total.

C. **Continued Authorization:** No dose beyond a total of 18 infusions (six cycles) will be authorized.

IV. Moxetumomab pasudotox-tdfk (Lumoxiti) is considered investigational when used for all other conditions not stated above.

Position Statement

Summary

- Moxetumomab pasudotox-tdfk (Lumoxiti) is an intravenous (IV) targeted therapy used for the treatment of relapsed or refractory hairy cell leukemia (HCL).
- The intent of this policy is to cover moxetumomab pasudotox-tdfk (Lumoxiti) for the indications and regimen for which it has been shown to be safe and effective, as detailed in the coverage criteria.
- The evidence is limited to one low quality single-arm, open-label trial.
  - All subjects in the trial had relapsed or refractory hairy cell leukemia (HCL) despite at least two prior therapies, including treatment with cladribine or pentostatin (purine nucleoside analog).
  - The trial reported durable complete response rate as a surrogate endpoint in patients who received moxetumomab pasudotox-tdfk (Lumoxiti) as a monotherapy. This surrogate endpoint has not been shown to correlate with improved survival or quality of life in relapsed or refractory HCL.
- The National Comprehensive Cancer Network (NCCN) HCL guideline lists moxetumomab pasudotox-tdfk (Lumoxiti) as a treatment option for relapsed or refractory HCL that has progressed on two prior systemic therapies, including treatment with cladribine or pentostatin.
- Moxetumomab pasudotox-tdfk (Lumoxiti) can be covered for a maximum of 18 doses, based on the dose studied in the trial (0.04 mg/kg of on days 1,3, and 5 of 28-day cycles for a maximum of six cycles).

Regence Pharmacy Services performs independent analyses of oncology medication evidence. NCCN clinical practice guidelines assignment of a category 2a/b recommendation does not necessarily establish medically necessity. The Regence Pharmacy Services analysis and coverage policy may differ from NCCN clinical practice guidelines.

Clinical Efficacy

- A single, low quality, single-arm, open-label trial (N=80) evaluated moxetumomab pasudotox-tdfk (Lumoxiti) in patients with relapsed or refractory HCL who received at least two prior therapies, including treatment with cladribine or pentostatin.
- A durable complete response of 30% was reported in the trial. The median duration of durable complete response was not reached. It is not known if these patients have longer remissions, live longer, or have better quality of life than those who receive other treatment options as there are no direct comparative studies that evaluate any of these outcomes to date. [1]
- Additional evidence is needed to establish the clinical benefit (e.g., improved survival, improved quality of life) of moxetumomab pasudotox-tdfk (Lumoxiti).
- The National Comprehensive Cancer Network (NCCN) HCL guideline lists moxetumomab pasudotox (Lumoxiti) among several other therapies for relapsed or refractory HCL. It is specifically recommended for patients who have progressed on two prior systemic therapies, including treatment with cladribine or pentostatin. [2]
- Other NCCN recommendations for relapsed/refractory HCL include single agent chemotherapy ± targeted therapies, monotherapy targeted agents, and combination targeted therapies. [2]

Investigational Uses

- Based on its mechanism of action, moxetumomab pasudotox-tdfk (Lumoxiti) may have potential applications in other B-cell mediated cancers; [3] however, there is no currently published evidence supporting use in any other condition other than CD-22-positive B-cell HCL.
- NCCN guidelines do not list moxetumomab pasudotox-tdfk (Lumoxiti) as a treatment option outside of relapsed or refractory B-cell HCL setting.

Safety [4]

- To date, there is only short-term, non-comparative information available regarding the safety of moxetumomab pasudotox-tdfk (Lumoxiti).
- Moxetumomab pasudotox-tdfk has a boxed warning for capillary leak syndrome and hemolytic uremic syndrome. Other serious AEs include electrolyte abnormalities.
- The most common AEs (incidence ≥ 20%) in clinical trials included infusion related reactions, edema, nausea, fatigue, headache, pyrexia, constipation, anemia, and diarrhea.

Dosing [4]

- Moxetumomab pasudotox-tdfk (Lumoxiti) is given via intravenous infusion in a dose of 0.04 mg/kg on days 1, 3, and 5 of each 28-day cycle.
- Treatment is given for a maximum of six cycles (18 infusions); however, treatment may be stopped early for disease progression or unacceptable toxicity.

Cross References
None

Codes	Number	Description
HCPCS	J9313	Injection, moxetumomab pasudotox-tdfk, 0.01 mg

References

1. Kreitman, RJ, Dearden, C, Zinzani, PL, et al. Moxetumomab pasudotox in relapsed/refractory hairy cell leukemia. *Leukemia*. 2018 Aug;32(8):1768-77. PMID: 30030507
2. NCCN Clinical Practice Guidelines in Oncology. Hairy Cell Leukemia v.2.2021 [Updated March 11, 2021]. [cited 3/15/2021]; Available from: https://www.nccn.org/professionals/physician_gls/pdf/hairy_cell.pdf
3. National Institutes of Health, Clinicaltrials.gov [website]. [cited periodically]; Available from: www.clinicaltrials.gov
4. Lumoxiti (moxetumomab pasudotox-tdkf) [package insert]. Rockville, MD: Innate Pharma; April 2020.

Revision History

Revision Date	Revision Summary
4/22/2021	No criteria changes with this annual update.
7/22/2020	No changes to coverage criteria with this annual update.
4/22/2020	Added continuation of therapy language (no change to intent of coverage criteria).
10/23/2019	No changes to coverage criteria with this annual update.
1/31/2019	New policy (effective 4/1/2019). Limits coverage to patients with relapsed/refractory hairy cell leukemia.

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Medication Policy Manual | **Policy No:** dru565

Topic: Libtayo, cemiplimab-rwlc | **Date of Origin:** April 1, 2019

Committee Approval Date: September 19, 2024 | **Next Review Date:** 2025

Effective Date: January 1, 2025

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

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Description

Libtayo (cemiplimab-rwlc) is an intravenously administered programmed death receptor-1 blocking antibody (PD-1 inhibitor) that is used in the treatment of several different types of cancers.

Policy/Criteria

Most contracts require pre-authorization approval of Libtayo (cemiplimab-rwlc) prior to coverage.

I. Continuation of therapy (COT): Libtayo (cemiplimab-rwlc) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Libtayo (cemiplimab-rwlc) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) confirming that criterion A, B, or C below is met.

A. A diagnosis of **cutaneous squamous cell carcinoma** (cSCC) when criteria 1, 2, and 3 below are met:

1. Documentation that the disease is metastatic or is not curable with surgical excision or radiation therapy.

AND

2. Libtayo (cemiplimab-rwlc) will be used as monotherapy.

AND

3. No prior use of programmed death receptor-1 blocking antibody therapy (PD-1 inhibitors) or programmed death-ligand 1 blocking antibody therapy (PD-L1 inhibitors) [see *Appendix 1*].

OR

B. A diagnosis of **basal cell carcinoma** (BCC), **locally advanced or metastatic**, when criteria 1 and 2 below are met:

1. Prior hedgehog pathway inhibitor therapy [e.g., Odomzo (sonidegib), or Erivedge (vismodegib)] was not effective or was not tolerated, unless use of hedgehog pathway inhibitor therapy is not appropriate.

AND

2. No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

OR

C. A diagnosis of **non-small cell lung cancer** (NSCLC), **locally advanced (not candidates for surgical resection or definitive chemoradiation) or metastatic**, when criteria 1, 2, and 3 below are met:

1. No prior use of systemic therapy for locally advanced or metastatic disease.

AND

2. No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

AND

3. Libtayo (cemiplimab) will be used in one of the following settings (a or b):

a. As monotherapy for tumors that express PD-L1 with a Tumor Proportion Score of at least 50% (TPS $\geq$50%).

OR

b. In combination with platinum-based chemotherapy for tumors that do not have EGFR, ALK, or ROS1 aberrations.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Libtayo (cemiplimab-rwlc) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Libtayo (cemiplimab-rwlc) will be authorized for 24 weeks in doses up to 350 mg every three weeks, until disease progression.

C. Reauthorization: Authorization **shall** be reviewed at least every 24 weeks for documented benefit. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met. Specifically, documentation that the medication is providing clinical benefit, including disease stability or improvement, and lack of disease progression, based on an assessment of change in tumor burden. If there is documentation of

potential disease progression, a shortened authorization (up to three months) may be approved to allow time for clarification of response to Libtayo (cemiplimab-rwlc), including clinical re-evaluation of the patient and reimaging.

PLEASE NOTE: Additional doses of Libtayo (cemiplimab-rwlc) will not be authorized without a documented recent assessment by the treating provider (such as oncologist) with objective evidence of response to therapy, such as by re-imaging and use of iRECIST criteria.

IV. Libtayo (cemiplimab-rwlc) is considered not medically necessary when used for the treatment of cervical cancer.

V. Libtayo (cemiplimab-rwlc) is considered investigational when used for all other conditions.

Position Statement

Summary

- Libtayo (cemiplimab-rwlc) is an intravenously administered programmed death receptor-1 blocking antibody (PD-1 inhibitor) used in the treatment of several types of cancers.
- The intent of this policy is to cover Libtayo (cemiplimab-rwlc) in settings where it has been studied and shown to be safe and effective, as detailed in the coverage criteria, with consideration for other available treatment options.
    * Where there is lack of proven additional benefit and/or lack of demonstrated health outcome (such as overall survival or improved quality of life) relative to alternative therapies, use of Libtayo (cemiplimab-rwlc) alone or in combination with other therapies is not coverable ("not medically necessary" or "investigational").
    * It is important to note that the fact that a medication is FDA approved for a specific indication does not, in itself, make the treatment medically reasonable and necessary.
- Many of the clinical indications for immunotherapies (PD-1, PD-L1, and others) have been approved by the FDA and endorsed by clinical guidelines based on surrogate measures such as overall tumor response rate (ORR) and progression-free survival (PFS) which are not proven to accurately predict clinically important outcomes such as improved overall survival or improved quality of life.
- *PD-L1 expression testing*: is required for coverage of many clinical indications for PD-1 and PD-L1 inhibitors.
    * There are several ways in which PD-L1 expression can be defined. In addition, how PD-L1 expression is defined varies by tumor type and setting.
    * PD-L1 expression is determined by the FDA-approved companion diagnostic testing, based on both the specific PD-1/PD-L1 inhibitor and the tumor type.
    * However, PD-L1 test results are not interchangeable across PD-1/PD-L1 inhibitors and/or indications. There is no conversion available from one type of test to another, such as combined positive score (CPS) versus tumor proportion score (TPS) versus percent of tumor cells (TC). Therefore, the correct test must be conducted for proper selection of patient populations for a given use.
- National Comprehensive Cancer Network (NCCN) guidelines recommend Libtayo (cemiplimab-rwlc) as a potential option in each of the treatment settings listed in the coverage criteria. In general, NCCN recommendations parallel the FDA approved indications.
- The PD-1 and PD-L1 inhibitors have the potential to cause immune-mediated adverse reactions that can result in pneumonitis, colitis, hepatitis, endocrinopathies, and nephritis.
- The FDA-approved dose of Libtayo (cemiplimab-rwlc) is 350 mg IV every three weeks until disease progression.
- Optimal sequencing of chemotherapy and immunotherapy in many cancers is unknown or the data is evolving. At this time, sequential use of immunotherapies is not supported by

current evidence. Specifically, there is no evidence to support the sequential use of different PD-1 or PD-L1 inhibitors once there is disease progression on prior PD-1 or PD-L1 inhibitor therapy, as well as use of adjuvant PD-1/PD-L1 inhibitor after neoadjuvant PD-1/PD-L1 inhibitor therapy (unless explicitly listed in the coverage criteria). Therefore, the use of sequential courses of PD-1/PD-L1 immunotherapy is not coverable.

- There is a study that evaluates Libtayo (cemiplimab-rwlc) in recurrent cervical cancer; however, the manufacturer has withdrawn the application for this indication. Keytruda (pembrolizumab) already has an indication in this population.
- There are ongoing studies using Libtayo (cemiplimab-rwlc) in a variety of other cancers. However, although initial evidence may be promising, the potential for clinical benefit in these conditions is still being investigated.
- *Reauthorization Criteria*: When coverage criteria are met, Libtayo (cemiplimab-rwlc) is authorized for six months (24 weeks) of therapy, after which time documentation must be provided to establish that the medication is effective. Specifically, there must be documentation of clinical benefit, including disease stability or improvement and there is a lack of disease progression, based on an assessment of change in tumor burden. Documentation of benefit must include an assessment of the most recent imaging ("restaging scans") and/or re-biopsy by the treating oncologist.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy

Cutaneous Squamous Cell Carcinoma (cSCC)

- Two small low-quality, single-arm, non-comparative open-label trials evaluated Libtayo (cemiplimab-rwlc) in patients with cutaneous squamous cell carcinoma (cSCC) who were not candidates for curative surgical resection or radiation therapy. [1 2]
    * One trial (phase 1) included 16 patients with metastatic cSCC, and 10 patients with disease that had recurred after two or more prior surgical procedures and the investigator expected that curative resection would be unlikely, or surgery would result in substantial complications or deformity. The second trial (phase 2) included 59 patients with metastatic cSCC.
    * Approximately 57% of the subjects in the trials had prior systemic therapy, and about 82% had prior radiotherapy.
    * In the phase 1 trial, the objective response rate (ORR), the primary endpoint, was 50% [95% CI: 30, 70]. There were no complete responses.
    * In the phase 2 trial, the ORR was 47% [95% CI: 34, 61]. There were four (7%) complete responses.
    * The Libtayo (cemiplimab-rwlc) trials evaluated objective response rate (ORR) as a surrogate endpoint. ORR is a measure of tumor size (visible by physical observation or on x-ray) and is a combination of complete and partial responses. In advanced disease, ORR may not be representative of disease that has traveled to lymph nodes of other parts of the body, so it may not be an accurate measure of clinical benefit. To further complicate interpretation of these results, there were only four complete responses reported out of the 85 patients enrolled in the trial. The remainder were partial responses. There is currently no way to predict in advance who might achieve a complete response.
- It has not yet been determined if Libtayo (cemiplimab-rwlc) provides clinically meaningful benefit in cSCC as current studies have used surrogate measures such as overall tumor response rate (ORR) which are not proven to accurately predict clinically important outcomes such as improved overall survival or improved quality of life. There is no evidence that compares the safety and effectiveness of Libtayo (cemiplimab-rwlc) with any other therapy that may be used in the inoperable/metastatic cSCC setting. Libtayo (cemiplimab-rwlc) was only studied as a monotherapy (not in combination with other systemic therapy).
- Libtayo (cemiplimab-rwlc) has not been studied in patients who have received prior PD-1 inhibitor therapy.
- The quality of the currently available evidence is low. Additional evidence is needed to establish the clinical benefit (e.g., improved survival, improved quality of life) and the durability of effect of Libtayo (cemiplimab-rwlc).
- The National Comprehensive Cancer Center (NCCN) SCC guideline lists Libtayo (cemiplimab-rwlc) among possible therapies for patients with cutaneous SCC that is considered inoperable. Other potential options include radiation, and/or chemotherapy. [3]

Basal Cell Carcinoma (BCC)

- The available evidence for Libtayo (cemiplimab-rwlc) as a monotherapy in BCC is based on a small, single-arm trial (low-quality evidence) that enrolled 84 patients with locally advanced BCC (laBCC) and 48 patients with metastatic BCC (mBCC). [1 4 5]
    * All patients had prior therapy with a hedgehog inhibitor (HHI), the current standard of care for advanced BCC. Seventy six percent had disease progression on a prior HHI, 34% had intolerance to a prior HHI, and 10% had no better than stable disease while on HHI therapy.
    * The primary endpoint of the study was objective response rate (ORR). ORRs ranged from 21% in the mBCC population, to 29% in the laBCC population. There were no complete responses in the mBCC population, while five patients (6%) were considered to have a complete response in the laBCC group.
- As described above under cSCC, ORR is a surrogate endpoint that does not necessarily predict clinical benefit, such as improved overall survival or improved quality of life.
- Of note, the part of the FDA BCC indication for Libtayo (cemiplimab-rwlc) that refers to "or in whom a HHI is not appropriate" is not part of a population that was defined or enrolled in the clinical trial. There are no known objective parameters used to define this subpopulation.
- All patients in the trial were naïve to prior PD-1/PD-L1 inhibitor therapy. To date, there is no evidence to support the benefit of sequential PD-1/PD-L1 inhibitor therapy after disease has progressed on a prior therapy with these agents.
- HHIs and cemiplimab are the only systemic therapies available for the treatment of laBCC and mBCC. The NCCN Basal Cell Skin Cancer guideline recommends Libtayo (cemiplimab-rwlc) for patients who have been previously treated with a HHI or for whom a HHI is not appropriate. [3]

Non-Small Cell Lung Cancer (NSCLC)

Front-line therapy, as monotherapy – NSCLC:

- The evidence for Libtayo (cemiplimab-rwlc) as a front-line monotherapy for advanced NSCLC when tumors have a PD-L1 of at least 50% [tumor proportion score (TPS) ≥ 50%] is derived from an open-label, randomized controlled trial (N = 710) that compared it with standard platinum doublet chemotherapy (EMPOWER-Lung 1). [6]
    * The population included patients with locally advanced (stage IIIB or IIIC, 15%) or metastatic (stage IV, 85%) NSCLC. Patients were naïve to prior therapy for advanced disease and had TPS ≥ 50%.
    * Patients with EGFR mutations, ALK translocations, or ROS1 fusions were excluded from the trial because therapy with targeted agents is the standard front-line therapy in these populations.
    * The median overall survival (OS) in the Libtayo (cemiplimab-rwlc) treatment arm was superior to that in the cytotoxic chemotherapy arm (22.1 months and 14.3 months, respectively; HR 0.68 [95%CI: 0.53, 0.87], p = 0.0022).
    * Libtayo (cemiplimab-rwlc) was found to improve median overall survival (OS) relative to standard of care cytotoxic chemotherapy when used as a front-line therapy for advanced NSCLC when the TPS > 50%. However, its relative

effectiveness when compared to Tecentriq (atezolizumab) or Keytruda (pembrolizumab), which are also each approved as monotherapy in this setting, is not known. There is not head-to-head data that compares any of these agents with one another.

Front-line therapy, in combination with platin-based chemotherapy – NSCLC:

- Libtayo (cemiplimab-rwlc) was also approved as part of a front-line regimen for advanced NSCLC based on a randomized, double blinded, phase 3 trial that compared Libtayo (cemiplimab-rwlc) and placebo. Both arms were given in combination with four cycles of platinum-doublet chemotherapy (followed by pemetrexed maintenance as indicated) (EMPOWER-Lung 1). [7]
    * The population included patients with locally advanced (stage III, 14.8%) or metastatic (stage IV, 85.2%) NSCLC. Patients were naïve to prior therapy for advanced disease.
    * Patients were negative for therapeutically actionable genetic mutations (EGFR mutations, ALK translocations, or ROS1 fusions).
    * Patients were enrolled irrespective of PD-L1 expression (29.8% PD-L1 <1%) or histology (57.1% non-squamous).
    * Libtayo (cemiplimab-rwlc) was initiated with investigators' choice of histology-specific platin-based chemotherapy as induction (four cycles) and then continued as monotherapy versus platin-based chemotherapy induction followed by pemetrexed switch maintenance or best supportive care (BSC).
    * The Libtayo (cemiplimab-rwlc) treatment arm demonstrated improved overall survival relative to the placebo arm, with an 8.9-month improvement in median OS.
    * It was noted that the combination of Libtayo (cemiplimab-rwlc) with chemotherapy may add additional toxicity relative to either therapy alone.
- The evidence for Libtayo (cemiplimab-rwlc) in locally advanced or metastatic NSCLC as an add-on to front-line platinum-based chemotherapy is based on a phase 3, double-blind RCT (EMPOWER-Lung 3) that demonstrated a statistically significant and clinically relevant improvement in OS relative to standard-of-care platinum-based chemotherapy alone (placebo group). The median OS was 21.9 months [95% CI: 15.5, NE] and 13.0 months [95% CI: 11.9, 16.1] in the Libtayo (cemiplimab-rwlc) and placebo groups, respectively. [8]
- As with other PD-1/PD-L1 inhibitors in their many other treatment settings, there is no evidence to support the benefit of sequential PD-1/PD-L1 inhibitor therapy after disease has progressed on a prior therapy with these agents.
- The NCCN NSCLC guideline lists Libtayo (cemiplimab-rwlc) among several preferred, regimens in the population for which it is indicated. [3]

Reauthorization Criteria:

- When coverage criteria are met, Libtayo (cemiplimab-rwlc) is authorized for six months (24 weeks) of therapy, after which time documentation must be provided to establish that the medication is effective. Specifically, there must be documentation of clinical benefit, including disease stability or improvement and there is a lack of disease progression,

based on an assessment of change in tumor burden.

* The standard of care for evaluation of response to cancer immunotherapy, such as Libtayo (cemiplimab-rwlc), is use of the iRECIST criteria for assessment of tumor burden. [9]
* The iRECIST criteria include use of quantitative and qualitative criteria for assessment of change in tumor burden for target lesions and non-target lesions. [10]
    - Quantitative measurements for target lesions (tumor size and % change)
    - Qualitative evaluation for non-target lesions (present/disappeared/ unequivocal progression)
* Documentation of benefit must include an assessment of the most recent imaging ("restaging scans") by the treating oncologist. Given the complexity of the evaluation, including use of the iRECIST criteria, Libtayo (cemiplimab-rwlc) will not be reauthorized without an assessment of response to therapy, such a partial response (iPR), complete response (iCR), or stable disease (iSD).
* Use of immunotherapy may result in pseudoprogression, due to immune and T-cell activation, which can appear similar to tumor flare. If there is documentation of potential disease progression ["unconfirmed progressive disease (iUPD)"], a shortened authorization (up to three months) may be approved to allow time for clarification of response to Libtayo (cemiplimab-rwlc), including clinical re-evaluation of the patient and reimaging. Guidelines recommend reimaging for iUPD after 4-8 weeks.
* If a patient has confirmed, unequivocal new lesions (progression of disease, iPD), additional Libtayo (cemiplimab-rwlc) is not coverable. If a new lesion is equivocal, iUPD reassessment by the treating oncologist with repeat imaging would apply (as noted above).

Not Medically Necessary Uses

- Libtayo (cemiplimab-rwlc) was studied in recurrent cervical cancer where it was found to improve overall survival relative to single-agent chemotherapy. The manufacturer withdrew its application to expand use of Libtayo (cemiplimab-rwlc) in this population. Keytruda (pembrolizumab) is already approved for use in cervical cancer. [11]

Investigational Uses

- There is the potential for off-label use of Libtayo (cemiplimab-rwlc) based on its mechanism of action (immune checkpoint inhibition).
- There are currently no published clinical trials that evaluate Libtayo (cemiplimab-rwlc) outside of the settings described above.

Dosing [1]

- The FDA-approved dose of Libtayo (cemiplimab-rwlc) is 350 mg IV every three weeks until disease progression.
- The dose studied in the clinical trials was 3 mg/kg every two weeks, which differs from the FDA-approved dose.

Appendix 1: FDA-Approved PD-1 and PD-L1 Blocking Monoclonal Antibody Therapies [a]
Programmed death receptor-1 (PD-1) inhibitors
Jemperli (dostarlimab)
Keytruda (pembrolizumab)
Libtayo (cemiplimab-rwlc)
Loqtorzi (toripalimab)
Opdivo (nivolumab)
Tevimbra (tislelizumab)
Zynyz (retifanlimab-dlwr)
Programmed death-ligand 1 (PD-L1) inhibitors
Bavencio (avelumab)
Imfinzi (durvalumab)
Tecentriq (atezolizumab)

[a] Or as listed on the FDA.gov website

Appendix 2: FDA-Approved Hedgehog Pathway Inhibitors
Erivedge (vismodegib)
Odomzo (sonidegib)

Cross References
Imfinzi, durvalumab, Medication Policy Manual, Policy No. dru500
Keytruda, pembrolizumab, Medication Policy Manual, Policy No. dru367
Opdivo, nivolumab, Medication Policy Manual, Policy No. dru390
Tecentriq, atezolizumab, Medication Policy Manual, Policy No. dru463

Codes	Number	Description
HCPCS	J9119	injection, cemiplimab-rwlc (Libtayo), 1 mg

References

1. Libtayo (cemiplimab-rwlc) [package insert], Regeneron Pharmaceuticals, Inc.; Tarrytown, NY. April 2024.
2. Migden MR, Rischin D, Schmults CD, et al. PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous-Cell Carcinoma. *N Engl J Med.* 2018;379(4):341-51. PMID: 29863979
3. NCCN Drugs and Biologics Compendium (NCCN Compendium). [cited Updated Periodically]. 'Available from:' https://www.nccn.org/professionals/drug_compendium/default.aspx.
4. Product Dossier: Libtayo® (cemiplimab-rwlc), Basal Cell Carcinoma Supplement. Bridgewater, NJ; February 2021. Regeneron | Sanofi Genzyme. Date Reviewed: May 4, 2021.
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Revision History

Revision Date	Revision Summary
9/19/2024	**Effective 1/1/2025:** Changed reauthorization from 'may' to 'shall.' Operationally, all approvals will be for 24 weeks (6 months). Ongoing therapy (beyond 24 weeks) will be subject to reauthorization review every 24 weeks, for documentation of disease stability or improvement and lack of disease progression.
12/7/2023	Added coverage criteria for Libtayo (cemiplimab) as an add-on to front-line platinum-based chemotherapy when no EGFR, ALK, or ROS1 aberrations are present. [New indication]
6/15/2023	Added coverage criteria for advanced NSCLC, 1st line in combination with platinum-based chemotherapy (effective 7/15/2023).
12/9/2022	Effective 3/1/2023: • Updated standard language in policy. • Added cervical cancer as not medically necessary.
7/16/2021	Added coverage criteria for advanced basal cell carcinoma (BCC) and in the front-line treatment of advanced non-small cell lung cancer (NSCLC) when tumor expression of PD-L1 is at least 50% (TPS $\geq$ 50%), two newly FDA approved indications.
4/21/2021	• No changes to coverage criteria with this annual update. • COT language was updated (no change to intent of coverage criteria).
1/22/2020	Added continuation of therapy (COT) criteria (no change to intent of coverage criteria).
1/31/2019	New policy (effective April 1, 2019). Limits coverage to patients with the cutaneous squamous cell carcinoma (cSCC), the setting in which it was studied and has a labeled indication.

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Medication Policy Manual | **Policy No:** dru574

Topic: Azedra, iobenguane I 131 | **Date of Origin:** April 1, 2019

Committee Approval Date: June 20, 2024 | **Next Review Date:** 2025

Effective Date: September 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Azedra (iobenguane I 131) is a radioactive drug that is injected directly into the bloodstream and is used to treat rare neuroendocrine tumors, specifically pheochromocytoma or paragangliomas when surgery and chemotherapy are not a treatment option.

PLEASE NOTE: This policy is not intended to limit the use of Azedra (iobenguane I 131) for diagnostic use.

Policy/Criteria

Most contracts require pre-authorization approval of Azedra (iobenguane I 131) prior to coverage.

I. Continuation of therapy (COT): Azedra (iobenguane I 131) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Azedra (iobenguane I 131) may be considered medically necessary when there is clinical documentation (including, but no limited to chart notes) that criteria A, B, and C below are met.

A. A diagnosis of **pheochromocytoma or paraganglioma** (PPGL) that is locally unresectable or has distant metastases.

AND

B. Documentation of a prior positive MIBG (iobenguane) scan [also known as an iobenguane, metaiodobenzylguanidine (MIBG) scan].

AND

C. Documentation of one of the following clinical situations (1 or 2):

1. The patient is ineligible for curative surgery and has progressed on prior PPGL therapy (such as prior surgery, chemotherapy, radiation)

OR

2. The patient is ineligible for chemotherapy.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Azedra (iobenguane I 131) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Azedra (iobenguane I 131) may be authorized one-time for a maximum of two therapeutic doses [up to 18,500 MBq (500 mCi) per dose].

C. Additional doses (beyond two) are considered investigational.

IV. Azedra (iobenguane I 131) is considered investigational when used for all other conditions.

Position Statement

Summary

- Azedra (iobenguane I 131) is a radiolabeled norepinephrine analog indicated for the treatment of patients with iobenguane scan positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma (PPGL) who require systemic anticancer therapy.
- At lower doses Azedra (iobenguane I 131) is used as a diagnostic agent, this policy is not intended to limit diagnostic use.
- The intent of the policy is to provide coverage for the FDA-labeled indications, where it has been shown to be safe and effective.
    * Azedra (iobenguane I 131) is approved for the treatment of iobenguane scan positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma (PPGL) that has progressed on prior therapy for PPGL (such as prior surgery, radiation, chemotherapy) or are not candidates for chemotherapy and when curative surgery is not a treatment option. [1]
    * In the clinical trial, patients had to: [2]
        - Be at least 12 years old,
        - Fail a prior PPGL therapy OR were not candidates for chemotherapy or other curative therapies (such as surgery for pheochromocytoma)
        - Be on stable antihypertensive medication for pheochromocytoma-related hypertension for at least 30 days
- The NCCN Neuroendocrine and Adrenal Tumors guideline recognizes Azedra (iobenguane I 131) for primary treatment of locally unresectable PPGL or distant metastases, with prior positive iobenguane (MIBG) scan. [3]
- There are no clinical trials that have demonstrated a superior benefit of any therapies for the treatment of PPGL over first line treatment with surgery.
- The recommended therapeutic dose of iobenguane I 131 (Azedra) is no more than 18,500 MBq (500 mCi) administered at least 90 days apart for a total of two therapeutic doses. The safety and effectiveness of higher or more frequent doses have not been established. [1]
    * Azedra (iobenguane I 131) is administered intravenously as a dosimetric (diagnostic) dose, followed by two therapeutic doses administered at least 90 days apart.

* The recommended dosimetric dose of Azedra (iobenguane I 131) is no more than 185-222 MBq (5-6 mCi).

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy

- There is low confidence in the evidence of efficacy for Azedra (iobenguane I 131). Evidence is limited to one single-arm, phase 2, open-label trial which is insufficient to demonstrate cause and effect, given the absence of a comparator. [1] There is no information on the efficacy of iobenguane I 131 (Azedra) relative to any other therapy.
- The endpoint employed in the trial, percentage of patients who had at least a 50% decrease in antihypertensive medications, is a surrogate endpoint that may be relevant to symptomatic treatment of extra-catecholamine release but does not accurately predict the durability of effect of Azedra (iobenguane I 131) or its effect on any clinically relevant outcome such as overall survival or improved quality of life.
    * The reported result was that 17 patients out of 68 evaluable patients (25%) had at least a 50% decrease in antihypertensive medications for at least six months.
    * Flaws of this low confidence trial include lack of a meaningful health outcome, open-label study design, and lack of a comparator arm.
    * There is insufficient evidence to establish the efficacy of Azedra (iobenguane I 131) for the treatment of neuroblastoma. There are multiple trials listed in clincatrials.gov, published early phase clinical trials and a Cochrane review the concluded that there is a lack of compelling evidence for the efficacy of Azedra (iobenguane I 131) for the treatment of neuroblastoma. [4] Although the preliminary evidence is promising, larger, well controlled trials are needed to establish the safety and efficacy of Azedra (iobenguane I 131) in this setting.

Safety [1]

- Radiolabeled iobenguane I-131 has been available for decades in lower diagnostic doses. Adverse events at the lower diagnostic doses are well characterized. At the higher therapeutic doses, the safety profile is still emerging, especially as it relates to secondary malignancies and radiation exposure risk. There is insufficient evidence to determine the long-term or relative safety of Azedra (iobenguane I 131) at the therapeutic doses that have been approved for treatment. However, based on the severity of the disease and the lack of other treatment options in the unresectable, locally advanced or metastatic setting, individual patients may find the potential for benefit to outweigh the risk.
- There is no high-quality evidence to support more frequent dosing of Azedra (iobenguane I 131) in pheochromocytoma or paragangliomas (PPGL). Higher doses of iobenguane I 131 (Azedra) have not been proven in published clinical trials to be more effective or safer for treatment of PPGL.
- There are multiple drug interactions with Azedra (iobenguane I 131) that impact effectiveness and safety. This should only be prescribed a provider familiar with these interactions.

Cross References
BlueCross BlueShield Association Medical Policy, 6.01.60 - Therapeutic Radiopharmaceuticals in Oncology. [August 2023]

Codes	**Number**	**Description**
HCPCS	A9590	Iodine I-131 iobenguane (Azedra), therapeutic, 1 millicurie **(PA required)**
HCPCS	A9508	Iodine i-131 iobenguane sulfate (Azedra), diagnostic, per 0.5 millicurie **(No PA required)**

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Revision History

Revision Date	Revision Summary
6/20/2024	No criteria changes with this annual review.
12/7/2023	No criteria changes with this annual review.
12/9/2022	• Updated standard language in policy. • No changes to coverage criteria with this annual update.
1/20/2021	Updated continuation of therapy (COT) language. No changes to coverage criteria.
1/22/2020	Added continuation of therapy (COT) criteria (no change to intent of coverage criteria).
1/31/2019	New policy (effective 4/01/2019). Limits coverage to patients with iobenguane scan positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma (PPGL), the setting in which it was studied and has a labeled indication.

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Medication Policy Manual

Policy No: dru575

Topic: Fabry Disease Treatments

- Fabrazyme, agalsidase beta
- Galafold, migalastat
- Elfabrio, pegunigalsidase alfa

Date of Origin: April 1, 2019

Committee Approval Date: June 20, 2024

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IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Medications in this policy are used in the treatment of Fabry disease, a rare metabolic condition.

Policy/Criteria

Most contracts require pre-authorization approval of Fabry disease treatments prior to coverage.

I. Continuation of Therapy (COT): Fabry disease treatments may be considered medically necessary for COT when there is clinical documentation (including, but not limited to, chart notes) confirming that criteria A through C below are met:

A. One of the following are met:

1. For diagnoses NOT listed in the coverage criteria below, criteria (a and b) must be met:

a. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

b. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

2. For diagnoses listed in the coverage criteria below, criteria (a and b) must be met:

a. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

b. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

3. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

AND

B. **(For Fabrazyme [agalsidase beta] and Elfabrio [pegunigalsidase alfa] only)** Site of care administration requirements are met (refer to Medication Policy Manual, Site of Care Review, dru408).

AND

C. Administration, Quantity Limitations, and Authorization Period" below applies, as well as "Investigational Uses" for combination therapy.

Please note: *Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Fabry disease treatments may be considered medically necessary when there is clinical documentation that criteria A through E below are met.

A. A diagnosis of **Fabry disease** has been established by or in consultation with a specialist in endocrinology or genetics.

AND

B. The diagnosis has been confirmed by alpha-Gal A enzyme deficiency (< 30 % normal activity) **AND/OR** confirmation of GLA mutation.

AND

C. **(Fabrazyme [agalsidase beta] or Elfabrio [pegunigalsidase alfa] only)** Site of care administration requirements are met [refer to Medication Policy Manual, *Site of Care Review*, dru408].

AND

D. **(Galafold [migalastat] only)** The patient has an amenable galactosidase alpha gene (GLA) variant, based on in vitro assay data.

AND

E. **(Galafold [migalastat] only)** Fabrazyme (agalsidase beta) or Elfabrio (pegunigalsidase alfa) have been ineffective, contraindicated, or not tolerated.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Fabrazyme (agalsidase beta) and Elfabrio (pegunigalsidase alfa) coverable only under the medical benefit (as a provider-administered medication).

B. Regence Pharmacy Services considers Galafold (migalastat) coverable only under the pharmacy benefit (as a self-administered medication).

C. When pre-authorization is approved, treatments for Fabry Disease will be authorized in the following quantities:

TABLE 1.

Product	Quantity Limit
Fabrazyme (agalsidase beta)	Up to 26 infusions per year; ≤ 1 mg/kg every two weeks.
Elfabrio (pegunigalsidase alfa)	Up to 26 infusions per year; ≤ 1 mg/kg every two weeks.
Galafold (migalastat)	Up to 14 of the 123 mg capsules per 28 days.

D. Authorization **may** be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

IV. Combination use of any of the Fabry disease treatments is considered investigational.

V. Fabry disease treatments are considered investigational when used for any condition other than their FDA approved indications, as detailed in the coverage criteria above.

Position Statement

Summary

- Fabry disease treatments are intravenous (IV) or orally administered medications that are approved for use in Fabry disease and include the following:
    * Fabrazyme (agalsidase beta) and Elfabrio (pegunigalsidase alfa) are available as an IV infusion that provide exogenous sources of the deficient enzyme (alpha-Gal A) in patients with Fabry disease.
    * Galafold is an alpha-galactosidase A pharmacological chaperone indicated for the treatment of adults with a confirmed diagnosis of Fabry disease and an amenable galactosidase alpha gene variant based on in vitro assay data.
- Fabry disease is a rare, multi-system, X-linked, inborn error of glycosphingolipid metabolism caused by genetic mutation in the GLA gene resulting in partial or complete deficiency of the lysosomal enzyme alpha-Gal A. Deficiency in this enzyme results in the progressive intralysosomal accumulation of glycosphingolipids including globotriaosylceramide (GL3 or Gb3) in the kidneys, cardiovascular system, peripheral nerves, and the gastrointestinal tract leading to irreversible organ damage. It is chronic and slowly progressing. [1 2]
- The intent of this policy is to limit coverage of Fabry disease treatments for patients diagnosed with Fabry disease, confirmed by either an enzyme deficiency AND/OR positive GLA mutation, when prescribed by a specialist. Galafold (migalastat) may be covered when Fabrazyme (agalsidase beta) or Elfabrio (pegunigalsidase alfa) are ineffective or not a treatment option, as detailed in the coverage criteria.
- Galafold (migalastat) has only received an accelerated approval pathway based on reduction in kidney interstitial capillary cell globotriaosylceramide (KIC GL-3) substrate. this is a surrogate endpoint that is associated with a slower rate of progression of renal disease. [2] [1]
- Galafold (migalastat) has only demonstrated efficacy in patients with an amenable GLA variant that is interpreted by a clinical genetics professional as causing Fabry disease (pathogenic or likely pathogenic) in the clinical context of the patient. A list of amenable GLA variants is provided in the prescribing information or at http://www.fabrygenevariantsearch.com.
- Although one phase three study (the ATTRACT study) demonstrated that Galafold (migalastat) had efficacy in maintaining estimated glomerular filtration rate (eGFR) or measured GFR and significant decrease in left ventricular mass index compared to enzyme replacement therapy (ERT), its effect on more clinically meaningful outcomes such as overall survival, decreased incidence of end-stage renal disease, or cardiac events is uncertain.

- Fabrazyme (agalsidase beta), which has a full FDA approval, has a long history of use and has been demonstrated to reduce microvascular endothelial deposits of GL-3 and improve pain-related quality of life.
- Elfabrio (pegunigalsidase alfa) recently received a full FDA approval, showed comparable results in reducing kidney Gb3 deposits and slowing eGFR rates to Fabrazyme (agalsidase beta)., with both providing an exogenous source of alpha-Gal A enzyme
- While Galafold (migalastat) provides an oral option for the management of Fabry disease, it lacks long term safety and efficacy data.
- Fabrazyme (agalsidase beta) and Elfabrio (pegunigalsidase alfa) are administered intravenously every two weeks.
- The recommended dose of Galafold (migalastat) is 123 mg (1 capsule) by mouth once every other day at the same time of day. Higher doses have not been studied.
- The safety and efficacy of any of the Fabry disease treatments used in combination with each other has not been established. Galafold (migalastat) has not been studied in combination with enzyme replacement therapy for Fabry disease.
- Uniform recommendations for use of ERT in Fabry disease are not available, but guidelines based on the opinions of experts with experience in treating patients with Fabry's disease recommend that ERT be initiated as soon as possible in Type 1 (classic Fabry disease) and when clinical manifestations are observed in Type 2 (atypical Fabry disease).[3]
- Note: Galafold (migalastat) and Zavesca (miglustat) are distinct chemical entities. Zavesca (miglustat) is used in the treatment of Gaucher's disease.

Clinical Efficacy - Fabrazyme (agalsidase beta)

- Fabrazyme (agalsidase beta) is indicated for Fabry disease. A Cochrane Review A systemic review of nine trials comparing agalsidase alpha or beta in 351 participants, showed that when compared to placebo, ERT showed significant improvement regarding microvascular endothelial deposits of GL-3 and in pain-related quality of life. [4] Additionally, a double-blind, placebo-controlled, randomized, controlled trial conducted in 9 countries with Fabrazyme (agalsidase beta) demonstrated slowed progression to renal, cardiac, and cerebrovascular outcomes, and death. [5]
- Enzyme replacement therapy for Fabry disease as long history of use and a larger body of evidence for efficacy compared to Galafold (migalastat).
- Despite limited evidence to correlate improvement microvascular endothelial deposits of GL-3 with clinically meaningful outcomes there are limited treatment options for the management of Fabry disease.[6]

Clinical Efficacy – Elfabrio (pegunigalsidase alfa)

- Efficacy of Elfabrio (pegunigalsidase alfa) was established via two trials: F01/02, a phase 1/2 multicenter, single arm, open label trial with confirmatory supportive evidence from BALANCE, a phase 3 multicenter randomized, double blind, actively controlled trial.[5,7]

- In trial F01/F02, patients were infused with either 0.2 mg/kg, 1.0 mg/kg, or 2.0 mg/kg every 2 weeks for 3 months (F01) with 16 of the 18 patients enrolling in the extension phase (F02) for 9 additional months. All patients had confirmed symptomatic Fabry disease via alpha-Gal A enzyme deficiency or positive GLA mutation and were ERT naïve.[7,8]
    * The primary endpoint was reduction from baseline at 26 weeks in the average number of Gb3 inclusions via the Barisoni Lipid Inclusion Scoring System (BLISS), a quantitative biopsy scoring methodology that counts the actual number of Gb3 inclusions in each kidney peritubular capillary (PTC), then averages it across all the PTCs, with higher scores correlating to more severe disease. Gb3 scoring via the BLISS system is an accepted surrogate marker, used in the accelerated approval of migalastat (Galafold), however the correlation to providing clinically meaningful outcomes is unknown
    * Elfabrio (pegunigalsidase alfa) significantly reduced the mean Gb3 inclusions by 55% (-3.1) at 26 weeks, with a median reduction of 78% (-2.5).[8,9]
- The BALANCE study (n=77) compared Elfabrio (pegunigalsidase alfa) to enzyme replacement therapy with Fabrazyme (agalsidase beta) in patients with symptomatic and confirmed Fabry disease that had been on Fabrazyme (agalsidase beta) for at least 1 year prior to enrollment.[8,9]
    * Patients were randomized 2:1 to received Elfabrio (pegunigalsidase alfa) or Fabrazyme (agalsidase beta) both dosed at 1 mg/kg every 2 weeks for 2 years.
    * The primary endpoint was the annualized change from baseline in the eGFR slope at 24 months, a validated guideline accepted, and widely used surrogate endpoint.
    * Elfabrio (pegunigalsidase alfa) demonstrated comparable efficacy to Fabrazyme (agalsidase beta) in slowing eGFR decline (-2.4 vs -2.3 respectively) at two years.
    * However, non-inferiority to Fabrazyme (agalsidase beta) was not inferred by the FDA as there was a lack of previous data to determine the treatment effect of Fabrazyme (agalsidase beta) for this similar patient population in the BALANCE trial, such that the expected treatment effect of the active control is not well characterized.
- Elfabrio (pegunigalsidase alfa), an exogenous source of alpha-Gal A enzyme, demonstrated a significant improvement in the reduction of renal Gb3 inclusions in treatment naïve patients and displayed similar efficacy to the established standard of care ERT Fabrazyme (agalsidase beta) in the rate of annualized eGFR slope decline; However, these are surrogate endpoints that are not directly related to how a patients feels or functions.
- Elfabrio (pegunigalsidase alpha) has yet to prove an effect on clinically relevant outcomes including overall survival and quality of life measures. Long term efficacy data evaluating endpoints such as survival, decreased incidence of end-stage renal disease, or cardiac events are warranted.

Clinical Efficacy – Galafold (migalastat)

- Accelerated approval for Galafold (migalastat) was based on one phase-3 trial in patients 16 to 74 years of age with Fabry disease (the FACETS study).
- FACETS consisted of 3 parts: a 6-month double-blind, placebo-controlled treatment period, a 6-month open-label treatment period, a 12-month open-label extension phase to assess long-term outcomes. [10]
    * The primary endpoint was reduction in the average number of GL-3 inclusions in kidney interstitial. This is a surrogate endpoint that is associated with a slower rate of progression of renal disease, which provided the basis of accelerated approval.
    * The study enrolled 67 patients, however only 50 patients had amenable GLA variants. Results for were not statistically significant in the ITT population but
    * Among patients with an amenable variant, 52% of patients in the Galafold (migalastat) group had a ≥50% reduction in number of inclusions compared to 45% in the placebo group.
    * Additional studies are needed to confirm the benefit of Galafold (migalastat) on clinical outcomes.
- The ATTRACT study was an open-label, randomized, controlled study comparing Galafold (migalastat) to enzyme replacement therapy. Both treatments produced similar Reductions consisted of 3 parts: an 18-month open-label treatment period followed by a 12-month open-label optional extension to assess long-term outcomes. The primary endpoint was glomerular filtration rate (GFR). [11]
    * Galafold (migalastat) demonstrated similar efficacy to ERT in maintaining eGFR; however, longer term studies evaluating endpoints such as survival, decreased incidence of end-stage renal disease, or cardiac events are needed.

Genetic Testing [12][8]

- Galafold (migalastat) has only demonstrated efficacy in patients with an amenable GLA variant that is interpreted by a clinical genetics professional as causing Fabry disease (either pathogenic or likely pathogenic) in the clinical context of the patient. A list of amenable GLA variants is provided in the prescribing information or at http://www.fabrygenevariantsearch.com.

Investigational Uses

- The safety and efficacy of combination use with Fabry disease treatments has not been established. Fabry disease treatments have not been studied in combination with each other for Fabry disease. In clinical studies of Galafold (migalastat) and Elfabrio (pegunigalsidase alfa) patients were required to discontinue enzyme replacement therapy before enrolling in the treatment arm of the trials.

Cross References
Site of Care Review, Medication Policy Manual, Policy No. dru408
Enzyme Replacement Therapies, Medication Policy Manual, Policy No. dru426

Codes	Number	Description
HCPCS	J0180	Injection, agalsidase beta (Fabrazyme), 1 mg
HCPCS	J2508	Injection, pegunigalsidase alfa (Elfabrio), 1 mg

References

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12. Galafold [Prescribing Information]. Cranbury, NJ: Amicus Therapeutics; August 2018.

Revision History

Revision Date	Revision Summary
6/20/2024	• Updated HCPCS code for Elfabrio (pegunigalsidase alfa). • No criteria changes with this annual review.
9/14/2023	• Added newly FDA-approved Elfabrio (pegunigalsidase alfa) to current policy. • Updated coverage criteria to include confirmed Fabry disease diagnosis via enzyme deficiency (<30% alpha-Gal A activity) AND/OR genetic mutation of GLA gene.
6/15/2023	Updated quantity limit for Galafold to "Up to fourteen 123 mg capsules per 28 days" due to package size of 14 capsules (previously listed up to fifteen 123 mg capsules per 30 days).
6/17/2022	No criteria updates with this annual review.
7/16/2021	Updated continuation of therapy (COT) criteria (no change to intent of coverage criteria).
7/22/2020	Added continuation of therapy (COT) criteria (no change to intent of coverage criteria).
7/24/2019	• Moved Fabrazyme (agalsidase beta) to policy from dru426. Limits coverage to patients with Fabry Disease. • No change to intent of other coverage criteria. Clarification of policy language.
1/31/2019	New policy (effective 4/1/2019). Limits coverage to patients with Fabry Disease with an amenable GAL mutation in whom Fabrazyme (agalsidase beta) has been ineffective, not tolerated, or contraindicated.

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Medication Policy Manual | **Policy No:** dru577

Topic: Onpattro, patisiran | **Date of Origin:** April 1, 2019

Committee Approval Date: January 20, 2021 | **Next Review Date:** January 2022

Effective Date: April 1, 2021

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Patisiran (Onpattro) is used for treatment of polyneuropathy of hereditary transthyretin (hATTR)-mediated amyloidosis. Hereditary transthyretin-mediated amyloidosis is rare, progressive, hereditary disease caused by the buildup of abnormal protein deposits in the nervous system and major organs.

Policy/Criteria

Most contracts require pre-authorization approval of patisiran (Onpattro) prior to coverage.

I. Continuation of therapy (COT): Patisiran (Onpattro) may be considered medically necessary for COT when full policy criteria below are met, including site of care requirements, reauthorization criteria and quantity limit. Diagnostic criteria as well as the BASELINE functional status, including ADL limitations and/or polyneuropathy symptoms, prior to initiation of patisiran (Onpattro) must be provided.

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Patisiran (Onpattro) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes), that criteria A through F below are met.

A. Site of care administration requirements are met. [refer to Medication Policy Manual, Site of Care Review, dru408]

AND

B. A diagnosis of **hereditary transthyretin (hATTR) amyloidosis with polyneuropathy** established by a specialist in neurology, cardiology, amyloidosis, or genetics.

AND

C. The diagnosis has been confirmed by genetic testing, with documentation of a mutation in the transthyretin (TTR) gene.

AND

D. The patient has **Familial Amyloid Polyneuropathy (FAP)** Stage 1 or Stage 2 (*as defined in Appendix 1).*

AND

E. The patient has symptoms consistent with polyneuropathy (See *Appendix 2* for Symptoms of Polyneuropathy*).*

AND

F. The patient has not had a prior liver transplant

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers patisiran (Onpattro) to be a provider-administered medication.

B. When pre-authorization is approved, patisiran (Onpattro) be authorized in quantities as follow:

1. Patients weighing less than 100 kg: Up to 18 infusions in a one-year period based on dose of 0.3 mg/kg every 3 weeks

2. Patients weighing 100 kg or more: Up to 18 infusions in a one-year period based on dose of 30 mg every 3 weeks

C. Authorization shall be reviewed at least every six months. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, including stability or improvement in symptoms consistent with polyneuropathy.

IV. Patisiran (Onpattro) is considered investigational when used for all other conditions, including but not limited to:

A. Hereditary transthyretin amyloidosis without polyneuropathy.

B. In combination with inotersen (Tegsedi).

C. Other forms of amyloidosis.

Position Statement

Summary

- Patisiran (Onpattro) a small interfering RNA (siRNA) used in the treatment of polyneuropathy of hereditary transthyretin (hATTR) amyloidosis.
- The intent of the policy is to allow coverage of patisiran (Onpattro) for patients with a confirmed diagnosis of hATTR (by genetic testing), when there is documented symptoms due to polyneuropathy, similarly to how it was studied, as detailed in the coverage criteria.
- The efficacy of patisiran (Onpattro) was demonstrated in the APOLLO study, an 18-month, phase 3 randomized, placebo-controlled trial in patients with genetically confirmed hATTR amyloidosis and polyneuropathy (FAP Stage 1 or 2).
- Patients with a history of liver transplant were excluded from the clinical trial.[1,2]
- Patisiran (Onpattro) improved neurologic function and quality of life compared to placebo. [2]
- Genetic testing is required to confirm the diagnosis of hATTR amyloidosis.
- Patisiran (Onpattro) may be covered for up to 0.3 mg/kg every 3 weeks (up to a max of 30 mg IV for patients weighing 100 kg or more), the dose studied in clinical trials. [1] The safety and effectiveness of higher doses have not been established. [1]

- The safety and effectiveness of patisiran (Onpattro) in conditions other than polyneuropathy of hATTR have not been established.
- The safety and efficacy of patisiran (Onpattro) in combination with inotersen (Tegsedi) has not been established.

Clinical Efficacy

- Efficacy of patisiran (Onpattro) was demonstrated the APOLLO study, an 18-month, phase 3 randomized, placebo-controlled trial. [2,3] Patients were required to meet the following requirements for enrollment:
    * FAP stage 1 (mild ambulatory impairment) or stage 2 (ambulatory with assistance).
    * A diagnosis of hATTR confirmed by genetic testing and biopsy.
    * Symptoms of neuropathy, measured using the Neuropathy Impairment Score (NIS). The NIS is a tool used to measure motor, sensory, and reflex function.
    * Patients with a history of liver transplant were excluded.
- The primary endpoint was change in modified Neuropathy Impairment Score +7 (mNIS+7) from baseline. Change in Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QOL-DN) score was a secondary endpoint.[2,4]
    * The mNIS+7 is exam-based assessment of neuropathy which includes measures of nerve fiber conduction, sensory testing, and autonomic measures (postural blood pressure). Higher scores indicate worse neurologic function.
    * The Norfolk QOL-DN evaluates patients' perception of impairment with respect to physical functioning/large fiber neuropathy, activities of daily living, neuropathy symptoms, small fiber neuropathy, and autonomic dysfunction. Higher scores indicate poorer quality of life.
- Results showed that patisiran (Onpattro) improved neurologic symptoms and improved quality of life compared to placebo. There is limited data on effect of patisiran (Onpattro) on other end organ dysfunction associated with amyloidosis, such as cardiovascular outcomes or mortality.[2]

Investigational Uses

- There are no published clinical trials evaluating the safety or efficacy of patisiran (Onpattro) for the treatment of any condition other than polyneuropathy of hATTR.
- Trials of patisiran (Onpattro) excluded patients with prior liver transplant. It is unclear if patients who have received a liver transplant would experience benefit as they would not be expected to produce mutated transthyretin protein.

Appendix 1: Familial Amyloid Polyneuropathy (FAP) Staging[5]	
Stage	**Symptoms**
0	Asymptomatic
I	Mild, ambulatory, symptoms at lower limbs limited
II	Moderate, further neuropathic deterioration, ambulatory but requires assistance
III	Severe, bedridden/wheelchair bound with generalized weakness

Appendix 2: Symptoms of Polyneuropathy	
Peripheral sensorimotor polyneuropathy Symptoms	**Autonomic neuropathy symptoms**
Tingling or increased pain in the hands, feet, hands and/or arms,	Orthostasis
Loss of feeling in the hands and/or feet, numbness or tingling in the wrists,	Abnormal sweating
Loss of ability to sense temperature,	Sexual dysfunction
Difficulty with fine motor skills	Recurrent urinary tract infections
Seizures	Dysautonomia (constipation and/or diarrhea, nausea, vomiting, anorexia, early satiety)

Cross References
Tegsedi, inotersen. Medication Policy Manual, Policy No. dru579
Site of Care Review, Medication Policy Manual, Policy dru408

Codes	Number	Description
HCPCS	J0222	Injection, patisiran (Onpattro), 0.1 mg.

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Revision History

Revision Date	Revision Summary
01/20/2020	Clarified criteria II.E. to allow for coverage in patients with symptoms of polyneuropathy, as noted in *Appendix 2*. Removed functional impairment component.
01/22/2020	- Added continuation of therapy (COT) criteria (no change to intent of coverage criteria) - Clarify reauthorization criteria (including improvement of baseline symptoms)
1/31/2019	New policy (effective 4/1/2019). Limits coverage to patients with polyneuropathy of hereditary transthyretin amyloidosis, the setting in which it was studied and has a labeled indication.

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Medication Policy Manual

Policy No: dru589

Topic: Elzonris, tagraxofusp-erzs

Date of Origin: July 1, 2019

Committee Approval Date: September 19, 2024

Next Review Date: 2025

Effective Date: December 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Elzonris (tagraxofusp-erzs) is an intravenously administered CD123-directed cytotoxin for the treatment of blastic plasmacytoid dendritic cell neoplasm (BPDCN) in adults and in pediatric patients 2 years and older, a rare type of cancer.

Policy/Criteria

Most contracts require pre-authorization approval of Elzonris (tagraxofusp-erzs) prior to coverage.

I. Continuation of therapy (COT): Elzonris (tagraxofusp-erzs) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Elzonris (tagraxofusp-erzs) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) of a diagnosis of **blastic plasmacytoid dendritic cell neoplasm** (BPDCN).

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Elzonris (tagraxofusp-erzs) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Elzonris (tagraxofusp-erzs) will be authorized in quantities of up to five doses per 21-day cycle, until disease progression.

C. Authorization **may** be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

IV. Elzonris (tagraxofusp-erzs) is considered investigational when used for all other conditions, including but not limited to:

A. Acute Myeloid Leukemia (AML).

B. Myelodysplastic Syndrome (MDS).

C. Myelofibrosis (MF).

D. Chronic Myelomonocytic Leukemia (CMML).

Position Statement

Summary

- Elzonris (tagraxofusp-erzs) is a CD123-directed cytotoxin used for the treatment of blastic plasmacytoid dendritic cell neoplasm (BPDCN) in adults and in pediatric patients 2 years and older.
- The intent of this policy is to limit coverage of Elzonris (tagraxofusp-erzs) to patients diagnosed with BPDCN (in the front-line or relapsed/refractory setting), up to the dose shown to be safe and effective in clinical trials.
- There is low certainty in the evidence that Elzonris (tagraxofusp-erzs) improves complete remission/clinical complete remission (CR/CRc) when used in the front-line or relapsed/refractory setting of BPDCN based on one small, multi-cohort, open-label, single-arm trial.
- Typical treatment of BPDCN includes intensive chemotherapy followed by allogeneic stem cell transplant during the first remission based on low-quality, case series and retrospective reviews. The NCCN acute myeloid leukemia guideline lists Elzonris (tagraxofusp-erzs) as a potential therapy when used as part of intensive induction, and for patients with relapsed or refractory BPDCN.
- It is not yet known if the composite CR/CRc advantage seen with Elzonris (tagraxofusp-erzs) will translate to any clinically relevant benefit such as extended duration of remission or overall survival (OS) based on current trial results.
- The relative efficacy of the Elzonris (tagraxofusp-erzs) compared to multi-agent chemotherapy regimens is not known. There have been no direct comparisons of CR or OS benefit made to date.

- The safety and efficacy of Elzonris (tagraxofusp-erzs) in acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), myelofibrosis (MF), or chronic myelomonocytic leukemia (CMML) has not been established. Use in these settings is considered investigational.
- Use of Elzonris (tagraxofusp-erzs) in combination with other cytotoxic or targeted chemotherapy regimens has not been shown to improve its effectiveness.
- The National Comprehensive Cancer Network (NCCN) lists Elzonris (tagraxofusp-erzs) as an option in the population in which it is indicated in package labeling.
- Common adverse effects (AEs) reported with Elzonris (tagraxofusp-erzs) include capillary leak syndrome, nausea, fatigue, peripheral edema, pyrexia, and weight loss.
- The covered dose of Elzonris (tagraxofusp-erzs) is 12 mcg/kg IV over 15 minutes once daily on days 1 to 5 of a 21-day cycle. The safety and effectiveness of higher doses have not been established. Dose modifications may be necessary for severe AEs.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy

- The efficacy of Elzonris (tagraxofusp-erzs) for the treatment of BPDCN was evaluated in one, unpublished, prospective, multi-cohort, open-label, single-arm trial. [1,2]
    * The trial consisted of three stages: Stage 1 (lead-in, dose escalation), Stage 2 (expansion), and Stage 3 (pivotal, confirmatory). The review of efficacy was based primarily on the results of the Stage 3 cohort which included patients with treatment-naïve BPDCN.
    * Thirteen subjects were enrolled in the Stage 3 cohort which evaluated the composite endpoint CR/CRc rate, median CR/CRc and duration of CR/CRc.

    * CR/CRc was achieved in 54% of patients however median CR/CRc was not reached in the treatment group.
    * In a separate cohort of 15 patients with relapsed/refractory BPDCN, one patient achieved a CR (duration: 111 days) and one patient achieved CRc (duration: 424 days).
    * Evidence from this trial is of low quality due to the small, multi-cohort, open-label, single-arm design. Investigators and subjects were unmasked to treatment allocation.
    * Additionally, the composite CR/CRc endpoint has not been validated to accurately predict clinically relevant endpoints such as OS or quality of life.
- The treatment of BPDCN is addressed in the National Comprehensive Cancer Network (NCCN) acute myeloid leukemia (AML) guideline. The guideline lists Elzonris (tagraxofusp-erzs) among recommendations for BPDCN as a therapy for induction of intensive remission, and for patients with relapsed or refractory disease. [3]

Investigational Uses

- There are no published clinical trials evaluating the safety or efficacy of Elzonris (tagraxofusp-erzs) for the treatment of acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), myelofibrosis (MF), or chronic myelomonocytic leukemia (CMML). [4]
- Although a cohort in the pivotal trial included patients with AML, there is insufficient data to support the efficacy and safety of Elzonris (tagraxofusp-erzs) in this setting. [1]

Safety and Administration [1]

- The adverse events (AEs) observed with Elzonris (tagraxofusp-erzs) have the potential to be severe if not properly managed.
- Elzonris (tagraxofusp-erzs) has a box warning for capillary leak syndrome which may be life-threatening or fatal if not properly managed.
- Other serious AEs reported with Elzonris (tagraxofusp-erzs) include hepatotoxicity, nausea, fatigue, peripheral edema, pyrexia, and weight loss.
- The dose of Elzonris (tagraxofusp-erzs) is 12 mcg/kg IV over 15 minutes once daily on days 1 to 5 of a 21-day cycle. Dose modifications may be necessary for severe AEs (refer to prescribing information).

Codes	Number	Description
HCPCS	J9269	Injection, tagraxofusp-erzs (Elzonris), 10 micrograms

References

1. Elzonris® (tagraxofusp-erzs injection) [package insert]. Stemline Therapeutics, Inc.; New York, NY; July 2023.
2. Center for Drug Evaluation and Research. Medical Review: Elzonris (tagraxofusp-erzs) https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/761116Orig1s000MedR.pdf. Accessed February 1, 2019.
3. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology™. [Updated routinely]. [cited with policy updates and as necessary]. Available from: https://www.nccn.org/guidelines/category_1.
4. National Institutes of Health, Clinicaltrials.gov [website]. [cited periodically]. Available from: www.clinicaltrials.gov.

Revision History

Revision Date	Revision Summary
9/19/2024	No criteria changes with this annual review.
9/14/2023	No criteria changes with this annual review.
9/23/2022	There were no changes to the coverage criteria with this annual update.
10/15/2021	Updated continuation of care language. No change to the intent of the existing coverage criteria.
10/28/2020	• Continuation of care language was added to the policy. • There were no changes to the intent of the existing coverage criteria.
4/25/2019	New policy (effective 07/01/2019). Limits use of Elzonris (tagraxofusp-erzs) to patients diagnosed with BPDCN (in the front-line or relapsed/refractory setting), up to the dose shown to be safe and effective in clinical trials

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Medication Policy Manual | **Policy No:** dru590

Topic: Gamifant, emapalumab-lzsg | **Date of Origin:** July 1, 2019

Committee Approval Date: March 21, 2024 | **Next Review Date:** 2025

Effective Date: June 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Gamifant (emapalumab-lzsg) is a medication used in the treatment of a rare blood condition [hemophagocytic lymphohistiocytosis (HLH)]. It is given by intravenous (IV) infusion.

Policy/Criteria

Most contracts require pre-authorization approval of Gamifant (emapalumab-lzsg).

I. Continuation of therapy (COT): Gamifant (emapalumab-lzsg) may be considered medically necessary for COT when criterion A or B below is met.

A. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

OR

B. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Gamifant (emapalumab-lzsg) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A through D below are met.

A. A diagnosis of refractory primary **hemophagocytic lymphohistiocytosis (HLH)**, established by or in consultation with a hematologist.

AND

B. Documentation that at least one prior HLH treatment (see *Appendix A*) was ineffective, not tolerated, or all options are contraindicated.

***PLEASE NOTE:** Ineffective is defined as no clinical response or improvement after at least two weeks of treatment.*

AND

C. Gamifant (emapalumab-lzsg) will be used in combination with dexamethasone.

AND

D. The patient meets criteria for, and actively participates in, a health plan care management program.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Gamifant (emapalumab-lzsg) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Gamifant (emapalumab-lzsg) will be authorized as follows:

1. Initial starting dose of up to 1 mg/kg twice weekly, for up to a total of 8 weeks.

2. If there is insufficient response to starting doses, Gamifant (emapalumab-lzsg) may be authorized for up to 10 mg/kg/dose twice weekly (dose escalation may be requested through your health plan care manager).

3. Total maximum duration of therapy: 8 weeks, or until time of hematopoietic stem cell transplantation (HSCT). Any authorization beyond 8 weeks will be requested and coordinated through your health plan care manager.

IV. Gamifant (emapalumab-lzsg) is considered investigational when used for any other conditions, including, but not limited to:

A. Retreatment, defined as use for relapsed/refractory HLH on or after a prior course of Gamifant (emapalumab-lzsg) treatment.

B. Previously untreated (treatment-naïve) primary HLH.

C. Secondary HLH (such as HLH developed during malignancies).

V. Gamifant (emapalumab-lzsg) is considered not medically necessary when used beyond 8 weeks.

Position Statement

Summary

- The intent of this policy is to allow for coverage of Gamifant (emapalumab-lzsg) for treatment refractory primary hemophagocytic lymphohistiocytosis (HLH) as a bridge to hematopoietic stem cell transplantation (HSCT), the indication studied in trials, when conventional HLH treatments are ineffective, not tolerated, or use is contraindicated.
- Primary HLH is a rare, autosomal recessive condition. It is caused by a genetic lymphocyte defect, which leads to uncontrolled immune activation, inflammation, and overproduction of cytokines such as interferon-γ (IFNγ), interleukin 6 (IL-6), and interleukin 10 (IL-10). If left untreated, primary HLH is a fatal condition with a median survival of two months after diagnosis.
- Gamifant (emapalumab-lzsg) is a monoclonal antibody that binds to and inhibits IFNγ. It is to be used until HSCT can occur and is given in combination with dexamethasone.
- The safety and efficacy of Gamifant (emapalumab-lzsg) was established based on one single-arm clinical trial in patients with treatment refractory primary HLH. There was a 63% ORR at week 8, and 70% survived to receive a HSCT. Despite the promising short-term response, clinically meaningful long-term outcomes such as overall survival are unknown at this time.
- Gamifant (emapalumab-lzsg) was not sufficiently studied in patients with treatment-naive primary HLH as only seven treatment-naïve patients were included in the trials. Conventional treatment options including etoposide (HLH-94, HLH-2004) and anti-thymocyte-based therapies have demonstrated effectiveness in this population. The use of Gamifant (emapalumab-lzsg) as first line therapy is not recommended by the FDA at this time.

- Gamifant (emapalumab-lzsg) may be covered in doses up to 10 mg/kg twice weekly for 8 weeks or until HSCT (i.e., the dosing studied in trials). The efficacy and safety of higher doses, a longer treatment duration, or use for relapsed/refractory HLH after a prior course of Gamifant (emapalumab-lzsg) has not been established.

Clinical Efficacy

Refractory Primary Hemophagocytic Lymphohistiocytosis [1]

- One unpublished, phase 2/3, single arm, open-label trial evaluated Gamifant (emapalumab-lzsg) for the treatment of refractory primary HLH (n=27) and treatment-naïve primary HLH (n=7).
- According to the FDA, the number of treatment-naïve patients was too small to be used as confirmatory evidence in this population and only the refractory population was considered to be the primary analysis population.
    * Patients received Gamifant (emapalumab-lzsg) with dexamethasone for 8 weeks, or until HSCT, whichever occurred first.
    * The primary endpoint was overall response (ORR) at the end of treatment.
    * Treatment with Gamifant (emapalumab-lzsg), was associated with an overall response rate of 63% (17/27) in the refractory primary HLH treatment group.
    * A total of 70% (19/27) of patients treated with Gamifant (emapalumab-lzsg) survived to receive a HSCT.
- To date, there are no trials comparing Gamifant (emapalumab-lzsg) with other treatments, either as a first-line or refractory therapy. Therefore, the relative efficacy is unknown.

Treatment Guidelines[2 3]

- The Histiocyte Society published a treatment protocol and diagnosis guidelines for HLH in 2004. The etoposide-based treatment protocol is known as HLH-2004.
- The following therapies are recommended for treatment of primary HLH:
    * Initial therapy: systemic therapy consisting of etoposide, cyclosporine, dexamethasone, and methotrexate (if CNS activity suspected) for 8 weeks.
    * Therapy can be continued past 8 weeks until a matched donor is found, and hematopoietic stem cell transplantation (HSCT) can occur.
    * The optimal medications to use in salvage therapy, for patients who do not respond to conventional treatment options listed above, is unclear at this time. Options include the addition of antithymocyte globulin (ATG; thymoglobulin) or alemtuzumab.
- Primary HLH is characterized by frequent reactivations unless patients undergo HSCT. During a reactivation, intensification of the systemic therapy will often result in a response to treatment, but the only known cure of primary HLH is HSCT.
- Between 25-50% of patients will fail to achieve a complete response to the current standard of care therapy and will require additional treatments.
- The 5-year survival for HLH is 50-60% with the therapies mentioned above and HSCT.

- Conventional treatment protocols, such as etoposide- (HLH-94, HLH-2004) and anti-thymocyte-based therapies have all demonstrated effectiveness in treatment-naïve primary HLH.

Investigational Uses

- Although the American Society of Hematology (ASH) lists Gamifant (emapalumab-lzsg) as a reported salvage option in secondary HLH, there is no evidence for the safety and efficacy of Gamifant (emapalumab-lzsg) for use in patients with secondary HLH.[4] Studies are ongoing for use of Gamifant (emapalumab-lzsg) in secondary HLH.[5]
- There is no evidence to establish the safety or efficacy of Gamifant (emapalumab-lzsg) in patients with secondary HLH, treatment-naïve primary HLH, use greater than 8 weeks, or as retreatment after a previous course of Gamifant (emapalumab-lzsg) therapy.

Safety [1 6]

- The most common side effects (>20% incidence) experienced during clinical trials were infections, hypertension, infusion-related reactions, and pyrexia.
- There were seven deaths (26%) in patients who received Gamifant (emapalumab-lzsg), reported at the time of the data cut-off. Of the seven deaths, five occurred prior to receiving the HSCT, and two occurred after the transplant.
    * Of the pre-transplant deaths, four were the result of new infections or worsening of a pre-existing infection.
    * Post-transplant deaths were attributed to known post-transplant complications, graft versus host disease, and graft rejection.

Appendix A. Conventional Treatments Used for Primary Hemophagocytic Lymphohistiocytosis [1 2]	
HLH-94	Etoposide Dexamethasone Intrathecal methotrexate (if CNS involvement is suspected)
HLH-2004	Etoposide Dexamethasone Cyclosporine Intrathecal methotrexate (if CNS involvement is suspected)
Anti-Thymocyte Based Therapy	Anti-thymocyte globulin (ATG, thymoglobulin) Corticosteroid Cyclosporine Intrathecal methotrexate (if CNS involvement is suspected)

Campath (alemtuzumab)* may be considered, as a second line therapy. For the purposes of the coverage of Gamifant, only medications listed within the table above will be considered versus the coverage criteria for previous therapy.

* *Note: Campath is no longer commercially available but may be provided free of charge via the Campath Distribution Program.*

Codes	Number	Description
HCPCS	J9210	Injection, emapalumab-lzsg (Gamifant), 1 mg

References

1. FDA 2018. Technology Assessment: FDA Summary Review of Emapalumab. Issue date: December 20, 2018. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/761107Orig1s000TOC.cfm. Accessed on
2. Henter, JI, Horne, A, Arico, M, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatric blood & cancer*. 2007 Feb;48(2):124-31. PMID: 16937360
3. Bergsten, E, Horne, A, Arico, M, et al. Confirmed efficacy of etoposide and dexamethasone in HLH treatment: long-term results of the cooperative HLH-2004 study. *Blood*. 2017;130:2728-38. PMID: 28935695
4. La Rosee, P, Horne, A, Hines, M, et al. Recommendations for the management of hemophagocytic lymphohistiocytosis in adults. *Blood*. 2019;133:2465-77. PMID: 30992265
5. Clinicaltrials.gov. [cited (updated periodically)]; Available from: https://clinicaltrials.gov/.
6. Gamifant [Prescribing Information]. Waltham, MA: Novimmune SA; May 2022.

Revision History

Revision Date	Revision Summary
3/21/2024	No criteria changes with this annual review.
3/16/2023	No criteria updates with this annual review.
3/18/2022	No updates with this annual review.
4/21/2020	Updated COT language (no change to intent).
4/22/2020	No criteria changes with this annual update. Added COT.
4/25/2019	New policy. Effective 7/1/2019. • Limits coverage to patients with refractory primary hemophagocytic lymphohistiocytosis (HLH) as a bridge to hematopoietic stem cell transplantation (HSCT), when conventional HLH treatments are ineffective, not tolerated, or use is contraindicated, the setting in which it was studied in trials.

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Medication Policy Manual | **Policy No:** dru591

Topic: Zolgensma, onasemnogene abeparvovec-xioi | **Date of Origin:** July 5, 2019

Committee Approval Date: December 7, 2023 | **Next Review Date:** 2024

Effective Date: March 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Zolgensma (onasemnogene abeparvovec-xioi) is an adeno-associated virus (AAV) vector-based gene therapy which replaces the defective SMN1 gene. It is used in the treatment of spinal muscular atrophy (SMA), a rare neuromuscular condition that affects motor function. It is given as a single, one-time intravenous (IV) infusion.

Policy/Criteria

Most contracts require pre-authorization approval of Zolgensma (onasemnogene abeparvovec-xioi) prior to coverage.

I. Continuation of therapy (COT): Zolgensma (onasemnogene abeparvovec-xioi) may be considered medically necessary for COT when full policy criteria below are met, including quantity limit.

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Zolgensma (onasemnogene abeparvovec-xioi) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A through J below are met.

A. A diagnosis of **spinal muscular atrophy** (SMA), established by or in consultation with a pediatric neuromuscular specialist (pediatric neurologist or rehabilitation doctor).

AND

B. Genetic confirmation of bi-allelic SMN1 mutations and two or three copies of survival motor neuron 2 (SMN2).

AND

C. Anti-AAV9 antibody titers ≤1:50, as determined by ELISA binding immunoassay.

AND

D. Documentation of SMA associated symptoms if present. This is to include an assessment of baseline motor function, with objective function-based testing (such as with CHOP-INTEND score).

AND

E. The patient will be less than 2 years of age at the time of the Zolgensma (onasemnogene abeparvovec-xioi) infusion.

AND

F. Patient has NOT received prior SMA gene therapy.

AND

G. Documentation of comprehensive SMA care, including physical therapy, respiratory care, and nutrition support as part of the patient's care plan.

AND

H. The patient does not have advanced SMA, as defined by one of the following:

1. Complete paralysis of the limbs.

OR

2. Requires invasive ventilatory support, defined as a tracheotomy with positive pressure.

OR

3. Requires non-invasive ventilatory support for greater than 16 hours per day.

AND

I. The patient meets criteria for, and actively participates in, a health plan care management program.

AND

J. Zolgensma (onasemnogene abeparvovec-xioi) will be administered intravenously (IV).

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Zolgensma, onasemnogene abeparvovec-xioi coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Zolgensma (onasemnogene abeparvovec-xioi) will be authorized in quantities up to 1.1×10^{14} vg/kg IV once, for one treatment course per lifetime.

C. Additional infusions of Zolgensma (onasemnogene abeparvovec-xioi) will not be authorized.

IV. Zolgensma (onasemnogene abeparvovec-xioi) is considered investigational when used for all other conditions not specifically addressed in the coverage criteria above, including, but not limited to:

A. Other types of classic SMA not specified above.

B. Non-5q SMA (SMA due to genetic abnormalities other than on chromosome 5q).

V. Zolgensma (onasemnogene abeparvovec-xioi) is considered not medically necessary when used in combination with Spinraza (nusinersen) or Evrysdi (risdiplam).

Position Statement

Summary[1-4]

- Zolgensma (onasemnogene abeparvovec-xioi) is an adeno-associated virus (AAV) vector-based gene therapy which replaces the defective SMN1 gene.
- Spinal muscular atrophy (SMA) is a rare condition, in which a genetic defect in the survival motor neuron (SMN) 1 gene leads to progressive loss of motor neuron function, hypotonia, weakness, and chronic respiratory insufficiency.
  * Children with the most severe form (SMA type 1) have symptoms before the age of 6 months and do not reach motor milestones (like sitting unassisted). SMA type 1 is also called “infantile SMA” or Werdig-Hoffman disease.
  * Later onset SMA (such as SMA type 2 or 3) is diagnosed later (symptom onset after 6 months of age), when a child fails to meet a motor milestone. SMA type 2 is also called Dubowitz disease. SMA type 3 is also called Kugelberg-Welander disease.
- Zolgensma (onasemnogene abeparvovec-xioi) has limited clinical trial data in a very specific patient population. However, in the currently available data, there is evidence of

a clinical improvement in SMA-related symptoms (improvement in motor function) in a patient population where motor function of that level would not be expected.

- Currently available clinical trial data is limited to pre-symptomatic SMA patients with two or three copies of SMN2 and symptomatic SMA type 1 patients with two copies of the SMN2 gene.
    * A diagnosis of SMA was confirmed genetically with a bi-allelic SMN1 mutations.
    * Clinical trials of Zolgensma (onasemnogene abeparvovec-xioi) in patients older than 2 years of age via intrathecal route are ongoing.
    * In addition, the safety and efficacy of Zolgensma (onasemnogene abeparvovec-xioi) in patients with a different number of copies of SMN2 is unknown at this time.
    * Genetic testing is required to confirm of a diagnosis of classic SMA (5q SMA) and to rule out other causes of spinal muscular atrophy. Onset of SMA symptoms (such as failure to meet motor milestones) differentiates SMA types 1, 2, and 3. SMA type 1 has onset of symptoms prior to 6 months of age and is the most severe, progressive form of SMA.
    * Zolgensma (onasemnogene abeparvovec-xioi) has not been studied in patients with advanced SMA, such as complete paralysis of the limbs or disease that has progressed to the point of requiring permanent ventilation. This is defined as the use of invasive ventilatory support (tracheotomy with positive pressure) OR non-invasive ventilator support for greater than 16 hours per day. Patient with complete paralysis or significant ventilatory support were excluded from clinical trials.
- Patients with Anti-AAV9 antibody titers >1:50 (determined by ELISA binding immunoassay) were excluded from the trial due to the potential for these antibodies to render the AAV9 vector-based therapy ineffective.
- Guidelines recommend aggressive, comprehensive supportive care and monitoring of motor milestones with objective function-based testing (such as with a HINE or CHOP-INTEND score).
- Zolgensma (onasemnogene abeparvovec-xioi) is only coverable in patients who are less than 2 years of age by the date of Zolgensma (onasemnogene abeparvovec-xioi) administration.
- Zolgensma (onasemnogene abeparvovec-xioi) may be covered for up to one dose per lifetime. There is no data on the safety or efficacy of repeated doses.
- Zolgensma (onasemnogene abeparvovec-xioi) is administered via a single, weight based intravenous (IV) infusion. There is insufficient evidence to support the safety or efficacy of other routes of administration at this time.
- The use of Spinraza (nusinersen) or Evrysdi (risdiplam) after Zolgensma (onasemnogene abeparvovec-xioi) for patients with an incomplete response, defined as persistent SMA symptoms, may be effective. However, the use of Spinraza (nusinersen) for residual SMA symptoms after Zolgensma (onasemnogene abeparvovec-xioi) is considered not medically necessary. Given the very high cost of the Zolgensma (onasemnogene abeparvovec-xioi) and Spinraza (nusinersen) therapies, we are unable to cover both treatment options.

Clinical Efficacy

Spinal Muscular Atrophy Type 1[3]

- One, ongoing, open-label, phase III trial (SPR1NT) in pre-symptomatic pediatric patients (n=29) with two or three copies of SMN2, demonstrated promising results.
    * In the 2-copy cohort (n=14), 100% of patients were alive without the need for respiratory support, 100% could sit independently for > 30 seconds, and 64% were walking independently at 14 months.
    * Preliminary results for the 3-copy cohort (n=15) demonstrate a similar story, although the trial is ongoing in this subset.
- One, low confidence, phase 1, open-label, dose-escalation trial in symptomatic pediatric patients with SMA type 1. Patients either enrolled in a low dose cohort (n=3) or a high dose cohort (n=12). The high dose cohort received the proposed therapeutic dose.
    * The primary endpoint was safety, which was defined as the incidence of grade III or higher treatment related toxicity.
    * Secondary endpoints included changes in Children's Hospital of Philadelphia Infant Test of Neuromuscular Diseases (CHOP-INTEND) from baseline score and improvement of motor function and muscle strength.
        ▪ No major milestones were achieved in the cohort that received the low dose Zolgensma (onasemnogene abeparvovec-xioi).
        ▪ In the high dose cohort at 24 months, the following major milestones were achieved:
            - 11 out of 12 patients (92%) had head control and could sit unassisted for 5 seconds.
            - 9 out of 12 patients (75%) could roll over or sit unassisted for 30 seconds.
            - 7 out of 12 patients (58%) required no ventilatory support.
            - 6 out of 12 patients (50%) required no nutritional support.
            - 2 out of 12 patients (17%) could crawl, stand, and walk independently.
    * At two years, no patients in either cohort died or were put on permanent ventilation.
    * Trial data is largely limited to SMA type 1 patients less than 6 months of age. A single patient over 6 months received the proposed therapeutic dose and did not have a response to the treatment. This prompted a change in the inclusion criteria to only enroll patients less than 6 months of age at the time of the infusion.
- An unpublished phase 3 trial (n=22) in the symptomatic SMA type 1 population (the STR1VE trial), with encouraging preliminary results, is currently ongoing.

Treatment Guidelines[1 2]

- Guidelines recommend maximizing aggressive multidisciplinary care in patients with all types of SMA.

    * Therapy should be tailored to the patient's functional level (non-sitter, sitter, or walker) and is to include a proactive approach (often prior to symptoms begin) for the following: rehabilitation, orthopedic management, nutritional support, pulmonary management, and psychological/social support for impacted families.
    * Although uptake in these treatment guidelines have improved survival for all types of SMA, developmental milestones are rarely acquired after a diagnosis of SMA type 1 is made.
- Guidelines were updated in 2017, and do not address the role of Spinraza (nusinersen), Evrysdi (risdiplam), or Zolgensma (onasemnogene abeparvovec-xioi).
- SMA is included as part of the recommended newborn health screenings by the Secretary of the Department of Health and Human Services. The majority of US states have implemented this recommendation and a pre-symptomatic diagnosis will soon be the predominant phase of SMA disease identification.

Investigational Uses

- There are no published trials that establish the safety or efficacy of Zolgensma (onasemnogene abeparvovec-xioi) in patients over the age of two years, such as those with symptomatic type 3 or type 4 SMA.
- There is no evidence to establish the safety or efficacy of repeat doses of Zolgensma (onasemnogene abeparvovec-xioi). If medical necessity criteria are met, only a single dose of Zolgensma (onasemnogene abeparvovec-xioi) will be covered per lifetime.

Safety [3 5]

- During the pivotal clinical trial of Zolgensma (onasemnogene abeparvovec-xioi) (n=15), about 1/3 of patients had liver enzyme elevation.
- Although in the clinical trials and in postmarketing experience, asymptomatic aminotransferase elevations were very commonly reported in the managed access program and in the post-marketing setting, Cases of acute serious liver injury and acute liver failure including a few cases with fatal outcomes, have been reported.The most common side effects (>40% incidence) experienced during clinical trials were upper respiratory tract infections, vomiting, constipation, pyrexia, nasal congestion, and gastroesophageal reflux. These are common conditions seen in all patients with SMA, although it is unclear if this therapy worsens these conditions, due to a lack of a control group.
- Due to the small number of patients treated with Zolgensma (onasemnogene abeparvovec-xioi) during clinical trials, additional data is necessary to further define the safety profile.

Cross References
Spinraza, nusinersen, Medication Policy Manual, Policy No. dru485
Evrysdi, risdiplam, Medication Policy Manual, Policy No. dru647
BlueCross BlueShield Association Medical Policy, 5.01.28 - Treatment for Spinal Muscular Atrophy. [April 2023]

Codes	Number	Description
HCPCS	J3399	Injection, onasemnogene abeparvovec-xioi (Zolgensma), per treatment, up to 5x10^15 vector genomes
ICD-10	G12.0	Infantile spinal muscular atrophy, type I [Werdnig-Hoffmann]

Appendix 1. Distribution of SMN2 Copy Number by SMA Type Worldwide[4]

SMN2 Copy Number	Type I	Type II	Type III
1	**7%**	**<1%**	**0%**
2	**73%**	**16%**	**5%**
3	**20%**	**78%**	**49%**
4	**<1%**	**5%**	**44%**
5	**<1%**	**<1%**	**2%**
6	**0%**	**0%**	**<1%**

References

1. Mercuri E, Finkel RS, Muntoni F, et al. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. *Neuromuscular disorders : NMD.* 2018;28(2):103-15. PMID: 29290580
2. Finkel RS, Mercuri E, Meyer OH, et al. Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. *Neuromuscular disorders : NMD.* 2018;28(3):197-207. PMID: 29305137
3. Mendell JR, Al-Zaidy S, Shell R, et al. Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy. *The New England journal of medicine.* 2017;377(18):1713-22. PMID: 29091557
4. Kemper A, Lam K, Comeau A, et al. Evidence-based Review of Newborn Screening for Spinal Muscular Atrophy (SMA): Final Report (v5.2). In: HHS, ed. Washington DC: Health Resources and Services Administration, March 2018.
5. Zolgensma (onasemnogene abeparvovec-xioi) [prescribing information]. Bannockburn, IL: Novartis Gene Therapies; February 2023.

Revision History

Revision Date	Revision Summary
12/7/2023	No criteria changes with this annual review.
12/9/2022	No changes to coverage criteria with this annual update.
7/16/2021	Effective 8/15/2021: • Updated coverage criteria to allow for use of Zolgensma (onasemnogene abeparvovec-xioi) in genetically diagnosed SMA in patients with 2 or 3 copies of SMN2, including those diagnosed pre-symptomatically, up to 2 years of age. • Updated criteria to be inclusive of additional symptoms of advanced SMA, including complete paralysis of the limbs AND permanent respiratory support. • Removed clinical trial ineligibility requirement.
1/20/2021	Added combination use with Evrysdi (risdiplam) to not medically necessary uses.
4/22/2020	Modification of criteria pertaining to coverage of onasemnogene abeparvovec in patients with prior nusinersen use (*criteria F.*). Updated to include prior SMA gene therapy only.
6/26/2019	New policy. Effective 7/5/2019. Limits coverage to symptomatic SMA Type I patients with 2 copies of the SMN2 gene and will be less than 6 months of age at the time of the Zolgensma (onasemnogene abeparvovec-xioi) infusion, the setting in which it was studied in trials.

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Medication Policy Manual

Policy No: dru598

Topic: Medications for Thrombotic Thrombocytopenic Purpura (TTP)

- Adzynma (ADAMTS13, recombinant-krhn)
- Cablivi (caplacizumab-yhdp)

Date of Origin: October 1, 2019

Committee Approval Date: June 20, 2024

Next Review Date: 2025

Effective Date: September 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Cablivi (caplacizumab-yhdp) and Adzynma (ADAMTS13, recombinant-krhn) are injectable medications which inhibit von Willebrand Factor (VWF) from binding to platelets to treat specific rare blood disorders.

Policy/Criteria

Most contracts require pre-authorization approval of Cablivi (caplacizumab-yhdp) prior to coverage.

I. Continuation of therapy (COT): Medications for Thrombotic Thrombocytopenic Purpura (TTP) [as listed in Table 1] may be considered medically necessary for COT when full policy criteria below are met, including quantity limit.

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Medications for TTP may be covered as follows:

A. **Cablivi (caplacizumab-yhdp)** is considered not medically necessary for **acquired thrombotic thrombocytopenic purpura** (aTTP).

OR

B. **Adzynma (ADAMTS13, recombinant-krhn)** may be considered medically necessary when clinical documentation (including, but not limited to chart notes) confirming that criteria 1 through 4 below are met.

1. Diagnosis of **congenital TTP (cTTP)** confirmed by both of the following (a and b):

a. Genetic testing (mutation in the ADAMTS13 gene).

AND

b. Documented ADAMTS13 activity < 10% [a disintegrin and metalloprotease with thrombospondin type 1 motif, 13 (ADAMTS13) activity < 10%].

AND

2. Diagnosis has been made by a specialist (hematologist, rare hematologic disease specialist, oncologist, or intensive care unit specialist).

AND

3. Other TTP or TTP-like disorders have been ruled out, including, but not limited to, acquired TTP (aTTP), complement-mediated hemolytic-uremic syndrome (CM-HUS), infection associated hemolytic-uremic syndrome (IA-HUS), antiphospholipid syndrome (APLS) etc.

AND

4. For use of Adzynma (ADAMTS13, recombinant-krhn) ***as prophylaxis***, documentation of persistent/refractory cTTP, defined as meeting all of the following (a through c):

a. History of at least one documented acute TTP event in the last 12 months, defined as all of the following (during the event timeframe) (i and ii):

i. A drop in platelet count ≥ 50% of baseline or a platelet count less than 100 x 10^9/L

AND

ii. An elevation of lactate dehydrogenase (LDH) levels >2 times baseline or > 2 times upper limit of normal per laboratory values.

AND

b. The patient is currently receiving plasma-based *prophylaxis* therapy, unless contraindicated, not tolerated or ineffective.

PLEASE NOTE: plasma-based therapies include, but are not limited to, fresh frozen plasma (FFP), solvent/detergent (S/D) plasma, and factor VIII products.

AND

c. At the time of initiation of Adzynma (ADAMTS13, recombinant-krhn), the patient is NOT having an acute TTP event, with documentation of stability with both of the following (i and ii):

i. Platelet count greater than or equal to 100 x 10^9/L

AND

ii. Lactate dehydrogenase (LDH) levels less than 2 times the upper limit of normal (ULN).

III. Medications for TTP (as listed in *Table 1*) are considered investigational when used for all other conditions.

IV. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Adzynma (ADAMTS13, recombinant-krhn) coverable under the medical benefit (as a provider-administered medication).

B. Regence Pharmacy Services considers Cablivi (caplacizumab-yhdp) coverable under the pharmacy benefit (as a self-administered medication) OR coverable under the medical benefit (as a provider-administered medication).

C. When prior authorization is approved, each drug will be covered in the following quantities and for the following authorization periods outlined in *Table 1*.

Table 1:

Product	Authorization Limit
Adzynma (ADAMTS13, recombinant-krhn)	**Initial authorization:** • In quantities up to the FDA-recommended weight-based dose and frequency limits. • Authorization: **shall** be reviewed at 6 months to confirm that current medical necessity criteria are met and that the medication is effective. **Continued authorization:** • In quantities up to the FDA-recommended dose and frequency limits (prophylaxis dosing frequency may be adjusted from once every OTHER week to once weekly dosing based on clinical response to treatment). • Authorization **shall** be reviewed every 12 months. Ongoing coverage requires documentation, (including chart notes) that the medication is effective, including, but not limited to, reduction in clinical symptoms (fatigue, headache, abdominal discomfort, lethargy, loss of concentration etc.), reduction in number of acute TTP events (including subacute events), an improvement in platelet counts (see *Appendix 1*).
Cablivi (caplacizumab-yhdp)	Although the use of Cablivi (caplacizumab-yhdp) is considered "not medically necessary," if pre-authorization is approved, Cablivi (caplacizumab-yhdp) will be authorized as follows: **Initial authorization:** • In quantities of up to 31 of the 11 mg vials for the first 30 days based on a dosing of 22 mg on Day 1, followed by 11 mg daily for up to 30 days after Plasma Exchange (PLEX) has ended. **Continued authorization (after the first 30 days):** • Up to a maximum 1 vial (11mg) per day for 30 days after PLEX has ended. • Authorization **shall** be reviewed at 30 days. Ongoing coverage of Cablivi (caplacizumab-yhdp) requires clinical documentation, including chart notes which indicate PLEX duration and discontinuation date and that the patient is not experiencing a recurrence of aTTP. Recurrence defined as thrombocytopenia requiring PLEX re-initiation. If a patient experiences more than 2 recurrences of aTTP while on therapy, no further Cablivi (caplacizumab-yhdp) will be authorized.

	Dose continuation beyond 30 days post-PLEX as follows: • ATTP has stabilized: No additional caplacizumab will be authorized. • ATTP has not stabilized: A maximum total of twenty-eight 11-mg vials per 28-day supply may be authorized until time of aTTP stabilization. No additional caplacizumab will be authorized once aTTP has stabilized, or beyond 28 days, whichever occurs first. • Authorization **shall** be reviewed at 30 days post PLEX discontinuation. Ongoing coverage of Cablivi (caplacizumab-yhdp) requires clinical documentation, including chart notes, that indicate the following: o Patient is at high risk for a recurrence of aTTP defined as ADAMTS13 level <10%. **AND** o Immunosuppressive therapy has been optimized. Defined as restarting or increasing corticosteroid dose or starting other immunosuppressive treatments (such as rituximab).

Position Statement

Adzynma (ADAMTS13, recombinant-krhn)

- Adzynma (ADAMTS13, recombinant-krhn) is a recombinant form of the endogenous human enzyme, a disintegrin and metalloproteinase with thrombospondin motifs 13 (ADAMTS13), used to treat individuals with congenital TTP.
- The intent of this policy is to limit coverage of Adzynma (ADAMTS13, recombinant-krhn)to patients with genetically confirmed cTTP, when prescribed by a specialist, and refractory to standard of care agents (plasma-based therapies).
- Laboratory testing to establish the diagnosis of cTTP includes genetic testing for mutations in the ADAMTS13 gene, the finding of severe ADAMTS13 deficiency (<10% of normal activity), and the absence of autoantibodies ("inhibitors") to ADAMTS13.
- The current standard of care focuses on ADAMTS13 replacement for both prophylaxis and acute events, using infusions of commercially-available plasma-based therapies (fresh frozen plasma, solvent/detergent plasma, and less often, factor VIII products) to replenish absent or low levels of ADAMTS13.
- The approval of Adzynma (ADAMTS13, recombinant-krhn) was based on one small phase 3 study for prophylaxis and on-demand treatment in individuals with cTTP.
- The pivotal trial showed a reduction, albeit minimal, in the number of acute TTP events over 12 months in subjects receiving prophylactic Adzynma (ADAMTS13, recombinant-krhn) compared to various plasma based prophylactic therapies. However, there is still insufficient evidence to show whether Adzynma (ADAMTS13, recombinant-krhn) has an

effect on quality of life related, clinically significant outcomes, such as reduction of chronic daily symptoms, reduction of end-organ damage, reduction in recurrent acute exacerbations over a longer time period, or reduction of clinically meaningful sequelae of acute TTP events (stroke, transient ischemic attacks, myocardial infarction etc.).

- Most subjects in the prophylactic cohort (n=37) of the pivotal trial were receiving a prophylactic plasma-based therapy at baseline or had a history of at least one or more acute TTP events. Platelet and lactate dehydrogenase (LDH) levels were measured to ensure subjects were eligible for prophylaxis, were not experiencing an acute event and were clinically stable.
- Both the 2020 British Society of Hematology (BSH) and the 2023 International Society on Thrombosis and Hemostasis (ISTH) guidelines recommend plasma-based therapies such as fresh frozen plasma (FFP) and solvent/detergent (S/D) plasma as treatments for cTTP, for prophylaxis and acute TTP events. Factor VIII products are mentioned only as alternatives to FFP and S/D plasma.
- Plasma based therapies (FFP, S/D plasma, factor VIII products) provide the best value. Adzynma (ADAMTS13, recombinant-krhn) has not been proven to be substantially more effective or safer than plasma-based therapies but is much more costly.
- Adzynma (ADAMTS13, recombinant-krhn) may be covered for up to the FDA-recommended weight-based dose and frequency. The safety and effectiveness of higher doses or increased frequencies have not been established.
- The safety and effectiveness for Adzynma (ADAMTS13, recombinant-krhn) in conditions other than cTTP have not been established.
- Given that most patients who present with an acute TTP event will be hospitalized, coverage for acute ("on-demand") treatment with Adzynma (ADAMTS13, recombinant-krhn) will be reviewed as part of an inpatient hospital stay.

Cablivi (caplacizumab-yhdp)

- Cablivi (caplacizumab-yhdp) is a monoclonal nanobody used to treat adult patients with acquired thrombotic thrombocytopenic purpura (aTTP) in combination with plasma exchange (PLEX) and immunosuppressive therapy.
- The use of Cablivi (caplacizumab-yhdp) for aTTP is considered not medically necessary, given the lack of proven additional benefit versus PLEX and immunosuppressive therapy, the current standard of care, which is known to have a very high response rate.
- Caplacizumab was studied in one phase 3 trial in patients with aTTP. The trial demonstrated no clinically meaningful difference in the time to normalization of platelet count between caplacizumab and placebo-treated patients. All patients in the trial remained on their baseline standard of care treatment regimen, which consisted of PLEX and immunosuppressive therapy.
- Caplacizumab does not address the underlying pathophysiology of aTTP; therefore, its role in reducing long-term sequelae of aTTP, such as neurocognitive deficits, arterial hypertension, and major depression, is unknown at this time.
- Additional, long-term, controlled trials are needed to assess the safety of caplacizumab, as bleeding safety signals were noted during clinical trials.

- Despite a reduction in aTTP recurrence rate, there is insufficient evidence to establish that the addition of caplacizumab to aTTP treatment regimens provides any value over the current SOC in improving clinically relevant outcomes, such as improving survival or reducing thromboembolic (TE) events. Therefore, the use of caplacizumab in aTTP is considered not medically necessary.
- Although the use of Cablivi (caplacizumab-yhdp) is NMN, the doses studied in trials were not to exceed use 30 days past the end of PLEX.

Disease Background - aTTP

- Acquired thrombotic thrombocytopenic purpura (aTTP) is a rare hematologic condition, caused by a severe deficiency in ADAMTS13, a protease responsible for cleaving von Willebrand factor (VWF) multimers. Without being cleaved, VWF multimers bind to platelets and form large platelet-rich clots which lead to tissue ischemia and multiorgan dysfunction.
- A presumptive diagnosis of aTTP is made if patients present with thrombocytopenia and hemolytic anemia without any other obvious cause. aTTP is confirmed by the finding of severe ADAMTS13 deficiency (<10% of normal activity), and the presence of autoantibodies ("inhibitors") directed against ADAMTS13.
- The current standard of care (SOC) for aTTP is PLEX and immunosuppressive therapy, which has led to a survival rate of 80-90%. Despite this high survival rate, neurocognitive deficits, arterial hypertension, and major depression have been reported to be more prevalent in survivors of aTTP compared to healthy populations without aTTP.

Disease Background - cTTP

- Congenital thrombotic thrombocytopenic purpura (cTTP) is an ultra-rare, autosomal recessive disease that is caused by mutations in the gene encoding for ADAMTS13, an enzyme that cleaves von Willebrand factor (VWF) multimers. Severe deficiencies in the ADAMTS13 enzyme (< 10% of normal enzyme activity) can lead to the formation of large, platelet rich VWF multimers, which create thrombi that can lead to ischemic damage to multiple organs (brain, kidney, and heart).
- Laboratory testing to establish the diagnosis of cTTP includes genetic testing for mutations in the ADAMTS13 gene, the finding of severe ADAMTS13 deficiency (<10% of normal activity), and the absence of autoantibodies ("inhibitors") to ADAMTS13.
- The current standard of care focuses on ADAMTS13 replacement for both prophylaxis and acute events, using infusions of commercially available, plasma-based therapies (fresh frozen plasma, solvent/detergent plasma, and less often, factor VIII products) to replenish absent or low levels of ADAMTS13.

Clinical Efficacy [1-4]

Adzynma (ADAMTS13, recombinant-krhn)

- Evidence for the safety and efficacy of Adzynma (ADAMTS13, recombinant-krhn) comes from a phase 3, randomized, controlled, multicenter, open-label, 2-period crossover with a single arm continuation trial (N=42).
- Subjects in the prophylaxis cohort (n=37) were randomized 1:1 to receive 6 months of either intravenous plasma-based therapy weekly or every other week based on the regimen at enrollment or Adzynma (ADAMTS13, recombinant-krhn) 40IU/kg IV every other week, followed by 6 months of alternate treatment for each cohort. Following this randomized crossover, 35 subjects entered the single arm continuation trial for 6-months and received Adzynma (ADAMTS13, recombinant-krhn) 40IU/kg IV every other week only.
    * The primary endpoint was the incidence of acute TTP events in the prophylaxis cohort. In the first 12 months, a single subject on plasma-based therapy had an acute TTP event, whereas there were no acute TTP events in subjects treated with Adzynma (ADAMTS13, recombinant-krhn). Due to minimal events captured, it is unknown whether Adzynma (ADAMTS13, recombinant-krhn) is substantially and meaningfully superior in reducing the incidence of acute TTP events, compared to plasma-based therapies.
    * Secondary endpoints were the incidence of subacute TTP events and incidence of TTP manifestations in the prophylaxis cohort (see Appendix 1, Definitions). There were fewer subacute and TTP manifestations in the Adzynma (ADAMTS13, recombinant-krhn) treatment groups compared to plasma-based therapy treated subjects, however, it is unclear what clinically meaningful outcomes these events relate to as they were defined by laboratory measures and subjective signs and symptoms only.
- Subjects in the *on-demand* cohort (n=5) were randomized 1:1 to receive treatment with either investigator-recommended plasma-based therapy or Adzynma (ADAMTS13, recombinant-krhn) for treatment of an acute TTP event, defined by laboratory values (see Appendix 1, Definitions).
    * Of the five acute TTP events in the on-demand treatment cohort, only two events met actual protocol criteria for acute TTP events. Of these two events, one was treated with Adzynma (ADAMTS13, recombinant-krhn), and the other with fresh-frozen plasma; both treatments led to acute TTP event resolution. Given the small number of acute TTP events captured, it is unknown whether Adzynma (ADAMTS13, recombinant-krhn) is superior to plasma-based therapies for the treatment of acute TTP events.
- While Adzynma (ADAMTS13, recombinant-krhn) corrects the underlying cause of cTTP (low enzyme activity), it is unknown what levels of repleted ADAMTS13 evoke what type of efficacy response. Peaks and troughs necessary to be maintained, if at all, have not been established to elucidate treatment impact on long-term organ damage, symptom reduction etc.
- It is unknown currently whether Adzynma (ADAMTS13, recombinant-krhn) has an effect on quality of life related, clinically significant outcomes, such as reduction of

chronic daily symptoms, reduction of end-organ damage, reduction in recurrent acute exacerbations over a longer time period etc.

- Efficacy and safety are unknown in the population of individuals who are not currently on prophylactic therapy (previously untreated patients), or those without a history of an acute TTP event, based on pivotal study inclusion criteria.
- Differences in plasma-based products at baseline and changing frequencies of their administration throughout the study could have confounded the outcome of this trial as these products inherently have various levels of ADAMTS 13 and are not standardized among trial treatment centers.

Cablivi (caplacizumab-yhdp)

- Evidence of efficacy for Cablivi (caplacizumab-yhdp) comes from one phase 3 double-blind, multicenter, placebo-controlled, randomized controlled trial. Patients were randomized to receive caplacizumab plus standard of care (SOC) (n=72) or placebo plus SOC (n=73) in the front line setting for aTTP. Treatment was continued for 30 days after the discontinuation of PLEX.
    * The primary endpoint was time to platelet count response, defined as a platelet count ≥ 150×10^9/L with subsequent stopping of daily plasma exchange (PLEX) within 5 days. There was a statistically significant improvement in the time to platelet count response (2.69 vs 2.88 days with placebo); however, the difference is not clinically meaningful.
    * Key secondary endpoints consisted of a composite of aTTP-related events [aTTP-related death, recurrence of aTTP, or a treatment-emergent major thromboembolic (TE) event].
        - Fewer patients had an aTTP-related event (12 vs 49% placebo), driven predominantly by a reduction in aTTP recurrence (4 vs. 38% placebo).
        - Recurrence was defined as a decrease in the platelet count requiring re-initiation of PLEX. It is important to note, that a change in platelet count is a surrogate endpoint with unknown clinical relevance.
    * There was no statistically significant improvement in overall survival or the rate of TE events in the caplacizumab versus placebo-treated groups during trials.
    * Although caplacizumab demonstrated improvement in platelet counts and a reduction in aTTP recurrence rate during the trial and short 28-day follow-up period, an earlier phase 2 trial demonstrated similar short-term results in recurrence rate. However, over the course of one year, there was no difference in recurrence rate between the caplacizumab and placebo-treated groups.
    * Differences in the immunosuppressive regimens and the baseline population between the treatment arms has the potential to confound the results of the trial.
- The pivotal phase 3 caplacizumab trial only included a 28-day follow-up period after treatment was discontinued. An ongoing follow-up trial is underway.
- There is insufficient evidence to establish that the addition of caplacizumab to aTTP treatment regimens improves any clinically meaningful outcomes, such as overall survival or a reduction in thromboembolic events, compared to the current SOC.

Guidelines [5-8]

- The British Committee for Standards in Hematology updated their guidelines in 2012 and recommend the following for management of aTTP:
    * Initiation of daily PLEX, continued for a minimum of 2 days after complete remission. This is defined as a normal platelet count (>150×10^9/L). Increased frequency of PLEX can be considered in refractory disease.
    * Intravenous or oral steroids should be started immediately after PLEX is initiated.
    * Rituximab should be considered in refractory patients or those with severe disease, including disease with neurological or cardiac symptoms.
    * Additional immunosuppressives, such as vincristine and cyclosporine, are generally reserved for aTTP refractory to other lines of therapy mentioned above.
    * The guidelines have not been updated since the approval of caplacizumab.

- The 2023 British Society of Hematology (BSH) and the 2020 International Society on Thrombosis and Hemostasis (ISTH) recommend the following for management of cTTP:
    * For an acute TTP event, plasma infusion is recommended, given its greater reliability as a ADAMTS13 source (higher post treatment ADAMTS13 activity) compared to factor VIII products. Factor VIII products can be considered if plasma infusion is not an option.
    * For patients with cTTP who are in remission, prophylaxis with plasma infusion or a "watch and wait" strategy is recommended. The approach to prophylaxis is highly individualized, considering patient characteristics, preferences, and the overall clinical circumstances.
    * Factor VIII products are usually not recommended for most patients and are reserved for use when plasma infusion is not an option, given sparse, low quality efficacy evidence and their product specific, high variability in ADAMTS13 concentrations.
    * For patients with cTTP who are pregnant, prophylaxis treatment with plasma infusion over factor VIII products is recommended. There is no evidence from clinical trials to support the use of Adzynma (ADAMTS13, recombinant-krhn) in pregnancy.

Safety [9 10]

<u>Cablivi (caplacizumab-yhdp)</u>

- The overall safety profile appears to be moderate and manageable in the context of the disease; however, bleeding safety signals were noted during the caplacizumab trials. Bleeding events occurred in 58% of patients in the caplacizumab treated group, versus 43% of the placebo-treated group.

Adzynma (ADAMTS13, recombinant-krhn)

- The overall safety profile appears to be moderate and manageable, with the most common adverse events in > 5% of subjects treated with Adzynma (ADAMTS13, recombinant-krhn) being headache, diarrhea, migraine, abdominal pain, nausea and upper respiratory infections.
- There were no reported deaths in the clinical trial with either treatment, and no hypersensitivity events with Adzynma (ADAMTS13, recombinant-krhn) treatment.

Dosing[9]

Adzynma (ADAMTS13, recombinant-krhn)

Prophylactic Therapy:

- 40 IU/kg body weight IV once every other week
- May be adjusted to 40 IU/kg body weight IV once weekly based on prior prophylactic dosing regimen or clinical response.

Appendix 1: Definitions of cTTP-related events

Event Type	Definition
Acute TTP event	Drop in platelet count ≥50% of baseline or a platelet count <100 x 10^9/L AND an elevation of lactate dehydrogenase (LDH) more than 2 times baseline or more than 2 times upper limit normal (ULN)
Subacute event	Thrombocytopenia event or a microangiopathic hemolytic anemia event AND organ-specific signs and symptoms including but not limited to renal dysfunction events, neurological symptoms events, fever, fatigue/lethargy, and/or abdominal pain.
Thrombocytopenia event	Drop in platelet count ≥25% of baseline or a platelet count <150 x 10^9/L.
Microangiopathic hemolytic anemia (MAHA) event	Elevation of LDH more than 1.5 times baseline or more than 1.5 times the upper limit of normal (ULN).

Codes	Number	Description
HCPCS	J3590	Unclassified biologics [when specified as Adzynma (ADAMTS13, recombinant-krhn)]
	C9399	Unclassified drugs or biologicals [when specified as Adzynma (ADAMTS13, recombinant-krhn)]
HCPCS	C9047	Injection, caplacizumab-yhdp (Cablivi), 1mg.

References

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Revision History

Revision Date	Revision Summary
6/20/2024	No criteria changes with this annual review.
3/21/2024	Added Adzynma (ADAMTS13, recombinant-krhn) to policy. Limits coverage to prophylaxis for patients with genetically confirmed cTTP, when prescribed by a specialist, and the patient is currently receiving plasma-based *prophylaxis* therapy, unless contraindicated, not tolerated or ineffective. Policy renamed Medications for Thrombotic Thrombocytopenic Purpura (TTP).
6/15/2023	No criteria changes with this annual update.
6/17/2022	No criteria changes with annual update, revision of description to simplify (no change of intent of policy).
7/19/2021	No criteria changes with this annual update.
7/22/2020	Added continuation of therapy (COT) criteria (no change to intent of policy).
7/24/2019	New policy. Effective 10/1/2019. The use of Cablivi (caplacizumab-yhdp) for aTTP is considered not medically necessary given the lack of clinically meaningful benefit versus the current standard of care alone, which is known to have a very high response rate.

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Medication Policy Manual

Policy No: dru600

Topic: Polivy, polatuzumab vedotin-piiq

Date of Origin: November 15, 2019

Committee Approval Date: March 6, 2025

Next Review Date: 2026

Effective Date: May 1, 2025

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Polivy (polatuzumab vedotin-piiq) is an intravenously administered medication used in the treatment of diffuse large B-cell lymphoma (DLBCL).

Policy/Criteria

Most contracts require pre-authorization approval of Polivy (polatuzumab vedotin-piiq) prior to coverage.

I. Continuation of therapy (COT): Polivy (polatuzumab vedotin-piiq) may be considered medically necessary for COT when is clinical documentation (including, but not limited to chart notes) confirming that criteria A and B below are met.

A. One of the following (1, 2, or 3) is met:

1. For diagnoses NOT listed in the coverage criteria below, criteria a and b must be met:

a. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

b. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

2. For diagnoses listed in the coverage criteria below, criteria a and b must be met:

a. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

b. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

3. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

AND

B. The requested number of doses (cycles) is within the policy limits below (Note: doses (cycles) already administered will be counted towards the coverable maximum quantity).

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Polivy (polatuzumab vedotin-piiq) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A through C below are met.

A. A diagnosis of **diffuse large B-cell lymphoma, not otherwise specified** (DLBCL NOS).

AND

B. Polivy (polatuzumab vedotin-piiq) is used in one of the following settings (1 or 2):

1. Previously untreated DLBCL NOS when all of the following are met:

a. The DLBCL NOS is Stage II with extensive mesenteric disease, Stage II with stage-modified International Prognostic Index (smIPI) >1, or stage III or IV.

AND

b. An International Prognostic Index (IPI) score of 2 or more.

AND

c. Polivy (polatuzumab vedotin-piiq) will be used in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone as part of the Pola-R-CHP regimen. *(The R-CHP regimen includes rituximab, cyclophosphamide, doxorubicin, and prednisone)*

OR

2. For relapsed or refractory DLBCL NOS when all of the following are met:

a. The disease is refractory to, or has progressed on or after, at least two prior chemotherapy regimens for DLBCL.

AND

b. The patient is not eligible for a stem cell transplant (SCT).

AND

c. Polivy (polatuzumab vedotin-piiq) will be given in combination with Treanda (bendamustine) and rituximab.

AND

C. The patient has not had prior therapy with Polivy (polatuzumab vedotin-piiq).

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Polivy (polatuzumab vedotin-piiq) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Polivy (polatuzumab vedotin-piiq) will be authorized for up to six infusions (cycles). No additional doses beyond the six initial infusions (cycles) will be authorized.

IV. Polivy (polatuzumab vedotin-piiq) is considered investigational when used for high-grade B-cell lymphoma (HGBL) and for all other conditions.

Position Statement

Summary

- The intent of this policy is to allow for coverage of Polivy (polatuzumab vedotin-piiq) in diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS) either in the front-line setting as part of the Pola-R-CHP regimen [Polivy (polatuzumab vedotin-piiq) plus rituximab, cyclophosphamide, doxorubicin, and prednisone] when patients have advanced-stage disease, or in the subsequent-line treatment setting when front-line treatment alternatives are not effective and stem cell transplant (SCT) is not an option, up to the dose shown to be safe and effective in trials.
- ***Treatment-naïve (front line) DLBCL NOS:*** Evidence is based on a fair quality randomized controlled trial (RCT) that compared Pola-R-CHP with R-CHOP [this regimen contains vincristine in place of the Polivy (polatuzumab vedotin-piiq)], the long-standing standard of care, in patients with advanced stage DLBCL NOS who had an International Prognostic Index (IPI) score of at least 2. Though progression-free survival (PFS) at two years was slightly higher in the Pola-R-CHP group, there was no difference in overall survival (OS). Investigators will continue to follow this data. A small cohort of patients with high grade B-cell lymphoma (HGBL) was included in this trial; however, it is unclear if potential benefit extends to this subpopulation based on current analyses.
- ***Relapsed or refractory DLBCL NOS:*** Evidence is based on a cohort of patients from a larger RCT (poor quality evidence) that compared the addition of Polivy (polatuzumab vedotin-piiq) to Treanda (bendamustine)/rituximab with Treanda (bendamustine)/ rituximab alone (control arm) in patients with refractory or relapsed DLBCL NOS who had a median of two prior therapies, and who were not candidates for a stem cell transplant. A higher number of complete responses (CR) was noted in the Polivy (polatuzumab vedotin-piiq) treatment arm at the end of therapy. This is not predictive of improvement in any clinical outcome (such as overall survival or quality of life) or durability of effect. Patients on Polivy (polatuzumab vedotin-piiq) experience a higher rate of side effects than those receiving Treanda (bendamustine) and rituximab alone.
- The NCCN B-cell lymphomas guideline lists Polivy (polatuzumab vedotin-piiq) among several possible options for patients with relapsed or refractory DLBCL who are not candidates for stem cell transplant. For patients with treatment-naïve disease, it lists both chemoimmunotherapy (R-CHOP) and Polivy (polatuzumab vedotin-piiq) plus chemoimmunotherapy (pola-R-CHP) as similar potential front-line options in patients with Stage III or IV DLBCL NOS who have an IPI $\geq$ 2.
- To date Polivy (polatuzumab vedotin-piiq) has primarily been evaluated in populations with a diagnosis of DLBCL NOS. Because DLBCL is a heterogeneous disease made up of different subtypes based on morphology, genetics, and biological behavior, additional studies in the other DLBCL subtypes are necessary before it can be established that Polivy (polatuzumab vedotin-piiq) is safe and effective in a broader DLBCL population.
- Polivy (polatuzumab vedotin-piiq) is administered intravenously in a dose of 1.8 mg/kg every three weeks for a total of 6 doses. A higher dose or a longer duration of therapy has not been shown to improve efficacy and may increase the risk of AEs.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy

Relapsed/refractory DLBCL (subsequent therapy)

- The efficacy of Polivy (polatuzumab vedotin-piiq) is based on a small cohort of patients from a larger, open-label study. Approval was via the FDA Accelerated pathway meaning a clinical benefit has not been established. The overall quality of the evidence is poor. [1-3]
    - The cohort (N = 80) included patients with relapsed or refractory DLBCL, not otherwise specified (NOS).
        - Patients received a median of two prior systemic therapies for their disease [approximately one-quarter (12 patients) had one prior therapy, one-quarter had two prior therapies, and one-half had three or more prior therapies].
        - Nearly all (98%) had prior therapy with an anti-CD20 agent.
        - Enrolled subjects were not candidates for an autologous stem cell transplant.
    - The study compared complete response rates (CR) achieved at the end of therapy (after six cycles) in patients who received Polivy (polatuzumab vedotin-piiq) plus Treanda (bendamustine)/rituximab [BR] with patients who received BR alone (control arm).
    - The complete response rate, an unvalidated radiographic endpoint, was 40% and 18% in the Polivy (polatuzumab vedotin-piiq) and control arms, respectively.

    * It is possible that the efficacy of Polivy (polatuzumab vedotin-piiq) is overstated. Exposure to Treanda (bendamustine) and rituximab was lower in the BR alone arm than in the Polivy (polatuzumab vedotin-piiq)/BR arm. Additionally, the response rates in the control arm (BR) of this study are approximately half of what has been reported in prior studies for BR in a similar population.

- *Guidelines*: The NCCN B-cell lymphoma guideline lists Polivy (polatuzumab vedotin-piiq) in combination with rituximab and bendamustine among treatment options for DLBCL that is refractory to, or relapsed after, prior therapy when patients are not eligible for a stem cell transplant. [4]

Front-line DLBCL (treatment-naïve)

- Polivy (polatuzumab vedotin-piiq) has subsequently been studied (POLARIX Study) in the front-line DLBCL treatment setting as an add-on to chemoimmunotherapy. [5]
    * Patients in the trial had CD20-positive, stage III or IV (89%) DLBCL NOS with an International Prognostic Index (IPI) score between 2 and 5 (two-thirds of participants had a score of 3 to 5 indicating intermediate-high- to high-risk disease). Patients with known CNS disease were excluded from the study.
    * The study compared Polivy (polatuzumab vedotin-piiq) plus rituximab, cyclophosphamide, doxorubicin, and prednisone (pola-R-CHP) with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). Therapy was given for up to six cycles (21-day cycles) in each treatment arm. Rituximab monotherapy was then continued for 2 additional cycles in each group.
    * Progression-free survival (PFS) at 2 years was 76.7% and 70.2% in the pola-R-CHP and R-CHOP treatment arms, respectively. There was no difference in overall survival (OS) at 2 years.
    * OS is the clinical endpoint of interest because PFS does not accurately predict clinical benefit.
    * The study included a subpopulation of patients with high-grade B-cell lymphoma (HGBL). However, because of the small size of this population, it is not known if potential benefits extend to this subgroup.
- *Guidelines*: The NCCN B-cell lymphoma guideline lists both Polivy (polatuzumab vedotin-piiq) plus R-CHP and R-CHOP as similar front-line treatment options for Stage III or IV (or Stage II with extensive mesenteric disease) DLBCL NOS in patients with an IPI $\geq$ 2. The guideline also notes that patients with Stage II disease with stage-modified International Prognostic Index (smIPI) >1 should be treated via the same pathway as patients with Stage III or IV disease. [4]
- There are no published studies that evaluate the efficacy of Polivy (polatuzumab vedotin-piiq) as a single agent.

Polivy (polatuzumab vedotin) as 'Bridging Therapy' for CAR T Therapy

- There are no well-conducted studies that directly compare Polivy (polatuzumab vedotin)-based regimens with chemotherapy-based regimens as a bridge to CAR T therapy for DLBCL. The available evidence is limited to a case series and one small, low-quality trial (n=42). Therefore, the relative efficacy of Polivy (polatuzumab vedotin)-based regimens versus chemotherapy-based regimens is not known. [6,7]

- There is no direct evidence demonstrating that Polivy (polatuzumab vedotin) is safer or better tolerated than chemotherapy-based bridging regimens. Polivy (polatuzumab vedotin) is. currently only indicated in combination with other chemotherapy (either BR or R-CHOP). Indirect comparisons across different studies may be confounded by differences in drug exposure and growth factor support.

Investigational Uses

- There is insufficient clinical trial evidence evaluating the safety or efficacy of Polivy (polatuzumab vedotin-piiq) outside of the DLBCL NOS treatment setting.t
- The use of Polivy (polatuzumab vedotin-piiq) in combination with anti-CD20 monoclonal antibodies other than rituximab is considered investigational. In the pivotal study, a small cohort of patients (N = 27) received Polivy (polatuzumab vedotin-piiq) plus Gazyva (obinutuzumab)/bendamustine in parallel to the Polivy (polatuzumab vedotin-piiq) plus BR and BR alone study arms; however, this data is of low quality and was not considered in the approval of Polivy (polatuzumab vedotin-piiq). [8] Furthermore, there is no evidence to establish the safety or efficacy of Gazyva (obinutuzumab) as a single agent in DLBCL.
- An early-phase, dose-expansion study evaluated the combination of Polivy (polatuzumab vedotin) in combination with Lunsumio (mosunetuzumab) in patients with relapsed or refractory large B-cell lymphoma (LBCL). The evidence is of low quality as it evaluated tumor response as a surrogate marker and did not employ any comparator arm. [9]
- The safety and efficacy of Polivy (polatuzumab vedotin-piiq) have not been established when:
    * Used as a monotherapy.
    * Used in doses higher than 1.8 mg/kg every 3 weeks for 6 infusions (total of 6 doses)

Safety [1]

- When Polivy (polatuzumab vedotin-piiq) is combined with Treanda (bendamustine) and rituximab:
    * The most commonly reported AEs are cytopenias and peripheral neuropathy.
    * The incidence of grade 3 or greater adverse effects (AEs) increases by approximately 10% over the use of Treanda (bendamustine) and rituximab alone [84% versus 74%, respectively].
- Based on current experience it appears that the safety and tolerability of Pola-R-CHP and R-CHOP regimens for DLBCL are similar. Cytopenia and nervous system AEs, including peripheral neuropathy, were numerically similar between the two regimens. R-CHOP may have a slight advantage over Pola-R-CHP with regard to gastrointestinal AEs.
- Strong CYP3A4 inhibitors may increase exposure to unconjugated monomethyl auristatin E (MMAE) [the anti-mitotic chemotherapeutic agent part of the polatuzumab vedotin-piiq molecule].

Dosing and Administration [1]

- Polivy (polatuzumab vedotin-piiq) is administered:
  - * As an intravenous infusion over 90 minutes. Premedication with an antihistamine and antipyretic is recommended. If tolerated, the rate of infusion can be decreased to 30 minutes on subsequent infusions.
  - * In a dose of 1.8 mg/kg every 3 weeks for six cycles total.
  - * In combination with Treanda (bendamustine) and rituximab
- There are recommendations to modify the dose of Polivy (polatuzumab vedotin-piiq) for peripheral neuropathy, infusion-related reactions, and cytopenias.

Appendix A: Subtypes of Diffuse Large B-cell Lymphoma (DLBCL) [4]
DLBCL, not otherwise specified (NOS)*
Follicular lymphoma (grade 3 only)
DLBCL coexistent with a low-grade lymphoma of any kind
Intravascular large B-cell lymphoma
DLBCL-associated with chronic inflammation
Anaplastic lymphoma kinase (ALK)-positive DLBCL
Epstein-Barr virus (EBV)-positive DLBCL in older patients
T-cell/histiocyte-rich large B-cell lymphoma

* This is the only subtype of DLBCL for which Polivy (polatuzumab vedotin-piiq) is covered

Cross References
Bispecific T-cell engager (BiTE) Therapies for B-cell lymphoma, Medication Policy Manual, Policy No. dru761
Chimeric Antigen Receptor (CAR) T-cell Therapies, Medication Policy Manual, Policy No. dru523
Monjuvi, tafasitamab-cxix, Medication Policy Manual, Policy No. dru652
Products with Therapeutically Equivalent Biosimilars/Reference Products, Medication Policy Manual, Policy No. dru620
Xpovio, selinexor, Medication Policy Manual, Policy No. dru607
Zynlonta, loncastuximab tesirine, Medication Policy Manual, Policy No. dru675

Codes	**Number**	**Description**
HCPCS	J9309	Injection, polatuzumab vedotin-piiq (Polivy), 1 mg

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Revision History

Revision Date	Revision Summary
3/6/2025	Extended coverage in front-line diffuse large B-cell lymphoma not otherwise specified (DLBCL NOS) to patients with Stage II with stage-modified International Prognostic Index (smIPI) >1.
3/21/2024	No criteria changes with this annual review.
9/14/2023	• Coverage criteria was added for Polivy (polatuzumab vedotin-piiq) in extensive stage II, or stage III or IV diffuse large B-cell lymphoma not otherwise specified (DLBCL NOS). • High-grade B-cell lymphoma (HGBL) was specifically listed as investigational.
3/16/2023	Added the use of Polivy (polatuzumab vedotin-piiq) in the front-line DLBCL setting in combination with chemoimmunotherapy as not medically necessary.
3/18/2022	• Made criterion IV (Investigational Uses) more general by removing specific conditions that might be considered investigational. • Combined allowed quantity and maximum number of infusions into one criterion (combined III.B and III.C). • Updated position statement to reflect guideline changes, etc.
4/21/2021	Updated COT. Clarification of criteria wording (no change to intent of coverage criteria with this annual update).
6/15/2020	Removed references to brand Rituxan from policy to account for upcoming changes in biosimilars policy (dru620).
4/22/2020	Added continuation of therapy (COT) criteria (no change to intent of coverage criteria).
10/23/2019	New policy (effective 11/15/2019). Limits coverage to patients with relapsed or refractory DLBCL NOS, the setting in which it was studied and has a labeled indication.

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Medication Policy Manual | **Policy No:** dru605

Topic: Spravato, esketamine | **Date of Origin:** August 15, 2019

Committee Approval Date: December 7, 2023 | **Next Review Date:** 2024

Effective Date: March 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Spravato (esketamine) is a nasal medication used for the management of treatment-resistant depression (TRD) or depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior. It is used in combination with an oral antidepressant. Spravato (esketamine) is administered under the supervision of a healthcare provider.

Policy/Criteria

Most contracts require pre-authorization approval of Spravato (esketamine) prior to coverage.

I. Continuation of therapy (COT): Spravato (esketamine) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, full policy criteria must be met for coverage.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1, 2 and 3 below must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. Attestation of evaluation by, or in consultation with, a board-certified psychiatric-mental health (PMH) prescriber [psychiatrist or PMH nurse practitioner (PMHNP)], and agreement with the use of Spravato (esketamine).

PLEASE NOTE: Attestation of previous PMH evaluation, at the initiation of Spravato (esketamine), may be used to establish medical necessity of this criterion.

AND

3. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. Spravato (esketamine) was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission, AND attestation of an evaluation by, or in consultation with, a board-certified psychiatric-mental health (PMH) prescriber [psychiatrist or PMH nurse practitioner (PMHNP)] and agreement with the use of Spravato (esketamine).

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Spravato (esketamine) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A, B, and C below are met:

A. Mental health provider assessment - One of the following is met (criteria 1 or 2):

1. The prescriber is a psychiatrist.

OR

2. The prescriber is not a psychiatrist, and both of the following are met (criteria a and b):

a. The patient is managed by, or in consultation with, a board-certified psychiatric-mental health (PMH) provider [psychiatrist or nurse practitioner (PMHNP)].

AND

b. The board-certified PMH provider completes both of the following (criteria i and ii):

i. Establishes the coverable diagnosis [attestation].

AND

ii. Has evaluated the suitability of the patient for the use of and agrees with the treatment plan for Spravato (esketamine) [attestation].

AND

B. Diagnostic criteria - One of the following (criteria 1 or 2) are met, as outlined in clinical documentation (in chart notes):

1. Depressive symptoms in patients with a diagnosis of **major depressive disorder** (MDD) **with acute suicidal ideation or behavior**.

OR

2. A diagnosis of **treatment resistant major depressive disorder** (MDD), when all the following are met (criteria a and b):

a. Documentation that at least three different antidepressants from two classes were ineffective or not tolerated (see *Appendix 1*).

AND

b. Documentation of non-pharmacologic treatments (including but not limited to cognitive behavioral therapy (see *Appendix 2*).

AND

C. Use in combination with an antidepressant: Spravato (esketamine) will be used in combination with an oral antidepressant.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Spravato (esketamine) coverable only under the medical benefit (as a provider-administered medication).

B. **Quantity Limits** - When pre-authorization is approved, Spravato (esketamine) will be authorized in quantities as follows:

1. **Initial authorization (Induction Phase)**: Up to 12 dose kits (56 mg or 84 mg per dose kit) in 8 weeks.

2. Continued authorization (Maintenance Phase): Up to 48 dose kits (56 mg or 84 mg per dose kit) in 48 weeks.

C. Authorization shall be reviewed as follows to confirm that medical necessity criteria are met, and that the medication is effective (criteria 1 and 2 below).

1. Authorization shall be reviewed as follows:

a. Initial authorization: Authorization shall be reviewed after 8 weeks.

b. Continued authorization (after the initial 8-week induction period): Authorization shall be reviewed at least every 48 weeks.

2. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, including all of the following (a through d):

a. Spravato (esketamine) continues to be used in conjunction with an oral antidepressant.

b. The patient has been re-evaluated and Spravato (esketamine) is providing clinical benefit evidenced by documented improvement or sustained improvement of depression symptoms.

PLEASE NOTE: Patient-specific symptoms must be provided, both current depression symptoms. Use of a depression symptom score (such as PHQ-9 or MADRS) may be used in the efficacy assessment.

c. Documentation that the current dose and frequency of Spravato (esketamine) is within the Quantity Limits (as stated above).

d. Use of doses of Spravato (esketamine) in excess of those listed above in the Quantity Limits are not coverable.

IV. Spravato (esketamine) is considered investigational when used for all other conditions, including but not limited to:

A. Depression other than listed in the coverage criteria above.

B. As an anesthetic agent.

Position Statement

Summary

- Spravato (esketamine) nasal spray is a non-competitive N-methyl-D-aspartate receptor antagonist that is used in combination with an oral antidepressant for the treatment of treatment-resistant depression (TRD), as well as depressive symptoms in patients with major depressive disorder (MDD) with acute suicidal ideation or behavior. [1]
- The intent of the policy is to cover Spravato (esketamine) for the treatment of TRD, as well as for depressive symptoms in patients with MDD with acute suicidal ideation (SI) or behavior, the indications where it has been studied and shown to be safe and effective, as detailed in coverage criteria.
- The efficacy of Spravato (esketamine) plus an oral antidepressant was evaluated as follows:

    * TRD: In three phase 3, randomized, controlled acute efficacy trials, as well as one maintenance trial. Patients had moderate to severe MDD and failed therapy with at least two other oral antidepressants. Once enrolled in the trial, patients received treatment with esketamine plus a newly assigned oral antidepressant or an oral antidepressant alone. [2]
- Depressive symptoms with MDD and SI: In two Phase 3, 4-week randomized, double-blind, placebo-controlled studies in adults with moderate-to-severe MDD (MADRS total score >28) who had active SI and intent. [2] In clinical trials, Spravato (esketamine) has only been studied as an adjunct therapy to oral antidepressants. The use of Spravato (esketamine) as a monotherapy is not coverable. [1]
- Guidelines recommend psychotherapy in combination with an oral antidepressant for the initial treatment for MDD. If there is no adequate response after optimizing the antidepressant dose for an adequate duration of time, switching to another antidepressant (from the same or different class), or combination with another antidepressant (from a different class) or non-antidepressant medication (lithium, thyroid hormone, a second-generation antipsychotic, or a stimulant) are recommended treatment options (see *Appendix 1*). [3]
- Spravato (esketamine) is dosed at 56 mg or 84 mg twice per week during the induction phase (weeks 1 to 4). Evidence of therapeutic benefit is evaluated at the end of the induction phase (at week 4) to determine the need for continued treatment. During the maintenance phase (beyond week 4), treatment is administered once weekly or every two weeks. [1]
- Because of the risk for sedation and dissociation after administration, Spravato (esketamine) must be administered under direct supervision of a healthcare provider, including a post-administration 2-hour observation period. [1,5] In addition, because the medication is for administration only by a REMS-certified provider, Spravato (esketamine) is not considered a self-administered medication. Therefore Spravato (esketamine) is coverable only under the medical benefit.
- The safety and effectiveness of Spravato (esketamine) in conditions other than TRD and depressive symptoms in patients with MDD with acute SI or behavior have not been established.

Clinical Efficacy

- The efficacy of Spravato (esketamine) for TRD was evaluated in three phase 3, randomized, controlled trials in patients with MDD. [4-6]
    * Patients were required to have a MADRS total score ≥28.
    * Patients failed therapy with at least two other antidepressants.
    * In the trial, patients had used an average of two prior antidepressants.
    * The trials compared treatment with Spravato (esketamine) plus a newly assigned oral antidepressant (duloxetine, escitalopram, sertraline, or venlafaxine) to an oral antidepressant alone for four weeks.
    * The primary endpoint in all three trials was the change from baseline in the MADRS total score.

    * Of the three trials, one trial demonstrated a significant difference between treatment with Spravato (esketamine) plus an oral antidepressant compared to the oral antidepressant alone.
- A long-term randomized, double-blind, maintenance study was also conducted in patients with TRD and determined that the time to relapse was delayed in patients treated with Spravato (esketamine) plus an oral antidepressant compared to an oral antidepressant alone. [1]
- The efficacy of Spravato (esketamine) for depressive symptoms with moderate-to-severe MDD and active SI was evaluated in two phase 3, 4-week randomized, double-blind, placebo-controlled studies. [7,8]
    * Patients were required to have a MADRS total score ≥28 and active suicidal ideation and intent.
    * All patients received comprehensive standard of care treatment, including an initial inpatient psychiatric hospitalization and a newly initiated or optimized oral antidepressant. Patients were on antidepressant monotherapy or antidepressant plus augmentation therapy (see *Appendix 1*).
    * Spravato (esketamine) plus standard of care demonstrated statistical superiority on the primary efficacy measure of the change from baseline in the MADRS total score at 24 hours after first dose (Day 2) compared to placebo nasal spray plus standard of care.
- In clinical trials, Spravato (esketamine) has only been studied as an adjunct therapy to oral antidepressants. The use of Spravato (esketamine) as a monotherapy is not coverable. [1]
- There is insufficient evidence to establish the safety or efficacy of dose escalation of Spravato (esketamine) beyond the doses in the FDA approved labeling (up to a maximum dose of 84 mg weekly). In addition, given the short half-life of Spravato (esketamine), the use of a repeat loading (full or partial) is not recommended for dose escalation. No published evidence was identified for higher doses or use of reloading. Therefore, the use of higher doses and/or a repeat loading dose is not coverable.
- There are various available antidepressant options, with several different mechanisms of action for treatment of MDD. There is no conclusive evidence that one antidepressant (within a class or between classes) is superior to other antidepressants, including use of augmentation medications (see *Appendix 1*) or Spravato (esketamine). However, Spravato (esketamine) is significantly more costly than other antidepressants, including many generics. Therefore, Spravato (esketamine) for TRD is coverable only when at least three antidepressant options, from at least two therapeutic classes, are ineffective or not a treatment option, when given as scheduled adequate therapeutic antidepressant doses. Of note: Some antidepressants (and augmentation therapies) may be used at much lower doses for sleep, management of pain, and other conditions. Therefore, the step therapy with lower-cost antidepressant treatment alternatives is met only when there is documented use of symptoms refractory to therapeutic antidepressant doses.
- MDD guidelines have not been updated for more than a decade. The 2010 American Psychiatric Association (APA) Guidelines recommend a stepwise approach to treatment of MDD with the following: [3]

    * For initial treatment for MDD, use of psychotherapy in combination with an oral antidepressant.
    * If inadequate response after optimizing the antidepressant dose for an adequate duration of time, switch to another antidepressant, from the same or different class.
    * Alternatively, use of the initial antidepressant in combination with another antidepressant (from a different class) or non-antidepressant medication (lithium, thyroid hormone, a second-generation antipsychotic, or a stimulant) are recommended treatment options (See *Appendix 1*).
    * Neither ketamine nor Spravato (esketamine) are included in the most recent guidelines (2010).

Investigational Uses

- The safety and effectiveness of Spravato (esketamine) in conditions other than those listed above (TRD or depressive symptoms with MDD with SI as detailed in the coverage criteria) have not been established.

Safety [1]

- The most common adverse reactions associated with Spravato (esketamine) are dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, increased blood pressure, vomiting, and feeling drunk.
- Because of the possibility of delayed or prolonged sedation and dissociation, Spravato (esketamine) must be administered under the direct supervision of a healthcare provider, including the administration period and the post-administration 2-hour observation period with each treatment session.
- Patients are not to engage in potentially hazardous activities, such as driving a motor vehicle or operating machinery, until the next day after a restful sleep.
- Spravato (esketamine) is only available through a restricted program under a REMS due to the serious adverse outcomes from sedation, dissociation, and abuse and misuse. [5] REMS certified pharmacies and distributors include, but are not limited to, facility (such as hospital) or specialty pharmacies such as home infusion pharmacies. Once REMS certified, providers should call 1-855-382-6022 to access information on how to obtain Spravato for their patient(s). [10]
    * A REMS-certified pharmacy will dispense (in person or ship) Spravato (esketamine) for a patient directly to the administering provider's office for storage and administration.
    * All REMS-certified providers must have a facility DEA number and the ability to "Maintain records on all shipments of SPRAVATO received and dispensing information including the patient name, dose, number of devices and date administered."

Appendix 1: An antidepressant (or treatment regimen) would include any of the following classes or combination of classes, given as scheduled adequate therapeutic antidepressant doses [3,9]				
TCAs [a]	SSRIs	SNRIs	Serotonin Modulators	Augmentation Medications
amitriptyline [b] desipramine doxepin imipramine nortriptyline protriptyline trimipramine	citalopram escitalopram fluoxetine fluvoxamine paroxetine sertraline vilazodone	desvenlafaxine duloxetine levomilnacipran milnacipran venlafaxine	nefazodone trazodone [b] vortioxetine	- lithium - liothyronine (Cytomel) - Atypical antipsychotics: aripiprazole, brexpiprazole, quetiapine, [b] olanzapine, risperidone - AEDs: carbamazepine, valproic acid, lamotrigine - Stimulants: methylphenidate, modafinil
		NE-Serotonin	MAOIs	
		mirtazapine	isocarboxazid phenelzine selegiline tranylcypromine	
		DNRI		
		bupropion [b]		

[a] Less frequently used, due to adverse event profile: clomipramine, maprotiline
[b] Antidepressant usual doses (mg/day): bupropion 300-450; trazodone 150-600; quetiapine 300. Lower doses are used for non-MDD indications, such as sleep.

Key: DNRI=dopamine norepinephrine reuptake inhibitor; MAOI=monoamine oxidase inhibitor; NE=norepinephrine; SNRI=serotonin norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant

NOTE: Documentation of duration of treatment and outcome of therapy to scheduled use of an adequate therapeutic dose for depression must be met.

Appendix 2: Psychotherapy methods to treat major depressive disorder may include, but are not limited to the following:
• Cognitive behavioral therapy (CBT) • Interpersonal therapy (IPT) • Psychodynamic therapy • Problem-solving therapy (in individual and group formats)

Cross References
BlueCross BlueShield Association Medical Policy, 5.01.34 - Esketamine Nasal Spray for Depression. [November 2023]
Transcranial Magnetic Stimulation as a Treatment of Depression and Other Disorders, Medical Policy Manual. Medicine, Policy No. 148.

Codes	**Number**	**Description**
HCPCS	G2082	Visit esketamine (Spravato) 56 mg or less
HCPCS	G2083	Visit esketamine (Spravato) > 56 mg
HCPCS	S0013	Esketamine (Spravato), nasal spray, 1 mg

References

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Revision History

Revision Date	Revision Summary
12/7/2023	• No criteria changes with this annual review.
12/9/2022	• Updated COT criteria to include PMH provider requirement. • Expanded prescriber requirement criterion to include PMHNP and reworded PMH provider assessment. • For operational consistency: Simplified antidepressant step therapy criterion, Updated Appendix 1 alternatives to align with guidelines. • Reworded reauthorization review criteria.
04/21/2021	Updated COT language wording (no change to intent). No other criteria changes with this annual update.
10/28/2020	Added coverage criteria for major depressive disorder (MDD) with acute suicidal ideation or behavior, a newly approved FDA indication. Clarified intent of other coverage criteria for MDD.
01/22/2020	Added continuation of therapy (COT) criteria (no change to intent of coverage criteria).
07/24/2019	New policy (effective 8/15/2019). Limits coverage to patients with treatment-resistant depression, the setting in which it was studied and has a labeled indication.

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Medication Policy Manual | **Policy No:** dru606

Topic: Vyondys 53, golodirsen | **Date of Origin:** August 15, 2019

Committee Approval Date: June 20, 2024 | **Next Review Date:** 2024

Effective Date: October 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Vyondys 53 (golodirsen) is an intravenous medication that may be used for Duchenne muscular dystrophy (DMD) when patients have a specific gene mutation. A clinical benefit, such as improved ambulation, of Vyondys 53 (golodirsen) has not been established.

Policy/Criteria

Most contracts require pre-authorization approval of Vyondys 53 (golodirsen) prior to coverage.

I. Continuation of therapy (COT): Vyondys 53 (golodirsen) is considered investigational for all conditions, per the full policy criteria below.

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Vyondys 53 (golodirsen) is considered investigational for all conditions, including Duchenne muscular dystrophy (DMD) that is amenable to exon 53 skipping (Table 1). However, if found to be medically necessary, criteria A must also be met:

A. Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, Site of Care Review, dru408].

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Vyondys 53 (golodirsen) coverable under the medical benefit (as a provider administered medication).

B. Although the use of Vyondys 53 (golodirsen) is considered investigational for all conditions, including DMD that is amenable to exon 53 skipping, if pre-authorization is approved, Vyondys 53 (golodirsen) will be authorized in doses up to 30 mg/kg every week (52 infusions per year).

C. Authorization shall be reviewed at least every twelve months for documented benefit. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met. Specifically, documentation that the medication is providing clinical benefit, including disease stability or improvement, and lack of disease progression.

Position Statement

Summary

- Vyondys 53 (golodirsen) is an intravenous therapy FDA approved for the treatment of Duchenne muscular dystrophy (DMD) when there is a confirmed mutation of the DMD gene that is amenable to exon 53 skipping. It was approved through the FDA Accelerated Approval Program based on an increase in dystrophin in skeletal muscles observed in some patients during a phase I/II trial. However, A clinical benefit of the drug, including improved motor function, improved strength, lack of disease progression (such as maintained ability to ambulate), and/or improved quality of life has not been established at this time. The FDA label states, "Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials."

- A clinical benefit (e.g. prolongation of independent ambulation, improved quality of life, or prevention of disease progression and disability) of Vyondys 53 (golodirsen) has not been established.
    * In one ongoing, open-label trial in a total of 25 patients, Vyondys 53 (golodirsen) was shown to increase dystrophin levels. However, it has not been proven that an increase in dystrophin will translate to improved clinical outcomes, such as improved motor function.
- The U.S. Centers for Disease Control and Prevention (CDC) has developed general management guidelines for DMD. The CDC recommends corticosteroids and supportive care to slow disease progression. These guidelines were published prior to the submission of Vyondys 53 (golodirsen) to the FDA, thus the use of Vyondys 53 (golodirsen) for DMD has not yet been addressed. [1-3]

Clinical Efficacy [4]

- Evidence regarding the effect of Vyondys 53 (golodirsen) on dystrophin levels is inconclusive. Data is limited to a small, unpublished, ongoing phase I/II trial; a placebo-controlled, two-part, dose escalation trial. Additional, larger, well-controlled trials are needed to establish the safety and efficacy of Vyondys 53 (golodirsen) in Duchenne muscular dystrophy (DMD).
- In the phase I/II trial, 12 patients were initially randomized to receive either placebo or Vyondys 53 (golodirsen) for 12 weeks. After 12 weeks, all existing patients and 13 newly recruited patients, received open-label Vyondys 53 (golodirsen) at a dose of 30mg/kg intravenously once weekly. Compared to baseline, the mean dystrophin levels increased by 0.918% of normal for the golodirsen-treated patients at 48 weeks.
    * Dystrophin production is a surrogate biomarker of disease improvement with an unknown correlation to health outcomes.
    * An absolute increase in dystrophin levels has not been correlated to improved ambulation or muscle function and a minimal clinically important difference in dystrophin levels has not yet been established. Experts have proposed that dystrophin levels greater than 10% of normal may be clinically meaningful; however, validation is needed.
    * The trial is ongoing (as of the date of FDA approval) to assess change in motor function. If the trial does not show an improvement in motor function, the FDA approval could be withdrawn.
- Although change in distance walked on a 6-minute walk test (6MWT) is a primary endpoint in the ongoing phase I/II golodirsen trial, the lack of a control group limits the clinical interpretation of the response. At week 144, the mean decrease in 6MWT was 99.0 m.[5]
- Vyondys 53 (golodirsen) has not yet been shown to improve any clinical outcomes such as quality of life, prolongation of independent ambulation, or prevention of disease progression and disability.

Safety

- The safety data is limited to very few patients included in the clinical trials. However, there was renal toxicity was observed in animals who received Vyondys 53 (golodirsen). The FDA label states, "Although renal toxicity was not observed in the clinical studies with VYONDYS 53, renal toxicity, including potentially fatal glomerulonephritis, has been observed after administration of some antisense oligonucleotides."[6]

Table 1: Mutations Amenable to Exon 53 skipping			
19-52	29-52	37-52	47-52
21-52	30-52	38-52	48-52
23-52	31-52	39-52	49-52
24-52	32-52	40-52	50-52
25-52	33-52	41-52	52
26-52	34-52	42-52	54-58
27-52	35-52	43-52	54-61
28-52	36-52	45-52	54-63

Cross References
BlueCross BlueShield Association Medical Policy, 5.01.27 - Treatment for Duchenne Muscular Dystrophy [June 2023]
BlueCross BlueShield Association Medical Policy, Gene Therapies for Duchenne Muscular Dystrophy [October 2023]
Exondys 51, eteplirsen, Medication Policy Manual, Policy No. dru480
Viltepso, viltolarsen, Medication Policy Manual, Policy No. dru640
Amondys 45, casimersen, Medication Policy Manual, Policy No. dru661
Elevidys, delandistrogene moxeparvovec, Medication Policy Manual, Policy No. dru754
Site of Care Review, Medication Policy Manual, Policy No. dru408

Codes	**Number**	**Description**
HCPCS	J1429	Injection, golodirsen (Vyondys), 10 mg
ICD-10	G71.0	Muscular dystrophy

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Revision History

Revision Date	Revision Summary
6/20/2024	Added Vyondys 53 to site of care (SOC) program (effective 10/1/2024).
12/7/2023	• Added quantity limit and reauthorization criteria (no change to intent) • Updated cross references.
12/9/2022	No criteria changes with this annual update.
1/20/2021	No criteria changes with this annual update.
1/22/2020	No criteria changes with this annual update.
12/13/2019	• Policy updated with brand name, based on FDA approval (on 12/12/19). • Added continuation of therapy (COT) criteria (no change to intent of coverage criteria).
7/24/2019	New policy. Effective 8/15/2019. Use of Vyondys 53 (golodirsen) is considered investigational in the treatment of all conditions, including Duchenne muscular dystrophy (DMD) that is amenable to exon 53 skipping. The available clinical trial data was insufficient to demonstrate safety or efficacy of Vyondys 53 (golodirsen) in the treatment of DMD.

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Medication Policy Manual **Policy No:** dru612

Topic: Anabolic Bone Medications **Date of Origin:** January 1, 2020

- Evenity, romosozumab
- Teriparatide (generic, Forteo)
- Tymlos, abaloparatide

Committee Approval Date: September 19, 2024 **Next Review Date:** 2025

Effective Date: December 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Medications included in this policy help with bone formation and are used to treat osteoporosis. Osteoporosis is when the bone becomes brittle and may lead to fractures.

Policy/Criteria

Most contracts require pre-authorization approval of anabolic bone medications prior to coverage.

I. Continuation of therapy (COT): Anabolic bone medications may be considered medically necessary for COT when criterion A, B, and C below are met.

A. One of the following (1, 2, or 3):

1. For diagnoses NOT listed in the coverage criteria below, full policy criteria must be met for coverage.

OR

2. For diagnoses listed in the coverage criteria below, criteria a and b must be met:

a. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

b. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

3. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

AND

B. For provider-administered medications: Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, Site of Care Review, dru408].

AND

C. When pre-authorization is approved, under COT, anabolic bone medications will be authorized using the dosing schedule for the cumulative lifetime approval duration found in *Table 1* below.

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Anabolic bone medications may be considered medically necessary when there is clinical documentation (including, but not limited to, chart notes) that criteria A through C below are met.

A. For provider-administered medications: Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, Site of Care Review, dru408].

AND

B. One of the following diagnostic criteria 1 through 4 below is met.

1. **For Evenity (romosozumab):** Diagnosis of **osteoporosis** with high risk of fracture as defined by meeting criteria a and b below:

a. Documented as postmenopausal.

AND

b. One of the following risks is present (criterion i or ii):

i. A bone mineral density that is 2.5 or more standard deviations below that of a "young normal" adult (T score at or below -2.5).

OR

ii. Current or history of at least one fragility fracture.

OR

2. **For Tymlos (abaloparatide):** Diagnosis of **osteoporosis** with high risk of fracture as defined by meeting criterion a or b below:

a. A bone mineral density that is 2.5 or more standard deviations below that of a "young normal" adult (T score at or below -2.5).

OR

b. Current or history of at least one fragility fracture.

OR

3. **For brand Forteo (teriparatide) and teriparatide (620mcg/2.48ml)**: Diagnosis of **osteoporosis or osteopenia** and both criteria a and b below are met:

a. Both generic teriparatide (**600mcg/2.4ml**) injection and Tymlos (abaloparatide) have been ineffective, contraindicated, or not tolerated.

AND

b. The patient is high risk for fracture as defined by meeting one of the following criterion (i, ii, or iii):

i. A bone mineral density that is 2.5 or more standard deviations below that of a "young normal" adult (T score at or below -2.5).

OR

ii. Current or history of fragility fracture.

OR

iii. Diagnosis of osteopenia (T-score between -1 and -2.5) and a history of glucocorticoid use for at least three months at a dose of 5 mg per day or higher of prednisone (or equivalent).

OR

4. **For generic teriparatide (600mcg/2.4ml)**: Diagnosis of **osteoporosis or osteopenia and** with high risk for fracture as defined by meeting criterion a, b, or c below:

   a. A bone mineral density that is 2.5 or more standard deviations below that of a "young normal" adult (T score at or below -2.5).

   OR

   b. Current or history of at least one fragility fracture.

   OR

   c. Diagnosis of osteopenia (T-score between -1 and -2.5) and a history of glucocorticoid use for at least three months at a dose of 5 mg per day or higher of prednisone (or equivalent).

AND

C. One of the following criteria 1 or 2 below is met:

1. The patient is at very high risk of fracture, defined as meeting one of the following criteria (a, b, or c) below:

   a. A history of multiple fragility fractures.

   OR

   b. A bone mineral density that is 3 or more standard deviations below that of a "young normal" adult (T score at or below - 3.0), with or without fracture history.

   OR

   c. A bone mineral density that is 2.5 or more standard deviations below that of a "young normal" adult (T score at or below -2.5) **and** a history of at least one fragility fracture.

OR

2. Step therapy with lower-cost alternatives has been ineffective, not tolerated or contraindicated as defined by at least one of the following (a through e):

   a. The patient has received at least three years of bisphosphonate therapy and remains at high risk for fracture.

   OR

   b. A bisphosphonate has been ineffective (e.g., a loss of BMD after at least 12 months of treatment or fracture while on treatment).

   OR

   c. Raloxifene was not effective after at least a 24-month treatment period, based on objective documentation (such as a reduction in T-score or fracture, despite 24-months of therapy).

   OR

   d. Bisphosphonates (both oral and IV) are documented as medically contraindicated, based on current medical literature and objective documentation (including, but not limited to, a creatinine clearance of less than 35 ml/minute).

   OR

e. Bisphosphonates (both oral and IV) are not tolerated due to documented clinical side effects.

PLEASE NOTE*:* In patients with underlying GI issues, use of oral bisphosphonates may be contraindicated or not tolerated. However, use of an IV bisphosphonate must be trialed for above criterion to be met.

IV bisphosphonates, such as zoledronic acid (generic Reclast), are available for coverage without pre-authorization.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Evenity (romosozumab) coverable only under the medical benefit (as a provider-administered medication).

B. Regence Pharmacy Services considers Tymlos (abaloparatide), teriparatide (generic [600mcg/2.4ml], Forteo), and teriparatide (620mcg/2.48ml) coverable only under the pharmacy benefit (as self-administered medications).

C. When pre-authorization is approved, anabolic bone medications will be authorized using the following dosing schedule for the cumulative lifetime approval duration listed below:

Table 1.

Medication	Dosing schedule	Cumulative lifetime approval duration	Administration
Tymlos (abaloparatide)	Up to 30 doses (80 mcg per dose) per month (one prefilled pen [1.56 ml total] monthly)	Up to 24 months	Self
teriparatide (generic 600mcg/2.4ml, Forteo)	Up to 28 doses (20 mcg per dose) per month (one prefilled pen [2.4ml total] monthly)	Up to 24 months	Self
teriparatide 620mcg/2.48ml	Up to 28 doses (20 mcg per dose) per month (one prefilled pen [2.48ml total] monthly)	Up to 24 months	Self
Evenity (romosozumab)	Up to one dose (210 mg per dose) per month (two prefilled pens [2.34 ml total] monthly)	Up to 12 months	Provider

D. When authorized, a maximum of 24 months will be approved as single agent (or in any combination) for (Tymlos, Forteo, teriparatide [600mcg/2.4ml], and teriparatide [620mcg/2.48ml]). Evenity (romosozumab) may be approved for a maximum of 12 months (as a single agent or in any combination). No further doses will be authorized beyond the cumulative lifetime approval duration listed above in *Table 1*.

E. Authorization **may** be reviewed at least annually to confirm that current medical necessity criteria are met, and that the medication is effective.

IV. Use of anabolic bone medications beyond one treatment course or for higher doses (as listed in *Table 1*) is considered not medically necessary.

V. Use of anabolic bone medications is considered investigational when used for all other conditions, including but not limited to:

A. Treatment of osteoporosis, other than listed in the coverage criteria above.

B. Prevention of osteoporosis.

C. To promote fracture healing.

D. To promote post-fusion healing.

E. Use in combination with denosumab (Prolia or Xgeva) or another anabolic bone medication (as listed in *Table 1*).

F. Sequential use, after therapy completion with other anabolic bone medication (as listed in *Table 1*).

Position Statement

Summary

- The intent of this policy is to limit coverage of anabolic bone medications for the indications and doses for which they have been shown to be safe and effective in trials, as detailed in the coverage criteria, when lower-cost standard of care treatment alternatives are not effective or use is contraindicated, or the patient is at very-high risk of fracture.
- Treatment decisions should be based on clinical information as well as intervention thresholds. When there is no demonstrated difference in safety or efficacy, the medication with the lowest cost often provides the best value for members.
- A T-score lower than -2.5 is diagnostic of osteoporosis. However, a non- or low- traumatic fracture (fragility fracture), is considered osteoporosis regardless of T-score. [1 2]
- Bisphosphonates (alendronate, risedronate, zoledronic acid, and ibandronate) for prevention of bone loss, regardless of cause, is the standard of care due to the body of evidence supporting efficacy and track record of safety. There are both oral and injectable bisphosphonates available as low-cost generics. Bisphosphonates and raloxifene have been shown to increase bone mineral density and reduce the incidence of fractures in patients with osteoporosis. [3-5] Risedronate and alendronate have been shown to be well-tolerated out to at least five years of therapy.
- There are many treatments for osteoporosis that are effective, have known long-term safety profiles, and are recommended by national treatment guidelines. Bisphosphonates represent the best value for the majority of patients.
- There is insufficient evidence to establish that any of the parathyroid hormone analog medications in this policy (Tymlos, Forteo, teriparatide [600mcg/2.4 ml], and teriparatide [620mcg/2.48 ml]) are safer or more effective than one another. [8] Of these products, generic teriparatide 600mcg/2.4 ml and Tymlos (abaloparatide) are lower cost options. As such, brand Forteo (teriparatide) and teriparatide (620mcg/2.48ml) are coverable only when these lower cost options are not a treatment option, as detailed in the coverage criteria.
- In a comparative trial, teriparatide had a lower rate of fractures as compared to risedronate; however, most patients were previously treated with osteoporosis medications such that the treatment affect may have been altered. [9]
- Preliminary data on sequential treatment suggests the use of the anabolic bone medications as first line therapy in high-risk patients followed by bisphosphonates may be more beneficial compared to bisphosphonates followed then by the anabolic bone medications: however, the data is limited to small trials, based only on bone density and not fracture risk reduction, and guidelines still recommend bisphosphonates as an option for initial treatment in high-risk patients.[8 10]
- American Association of Clinical Endocrinologists (AACE) guidelines recommend that Tymlos (abaloparatide), Prolia (denosumab), Evenity (romosozumab), teriparatide , and zoledronate as initial therapy for patients at very high fracture risk or for patients unable to use oral therapy. The definition for very high risk differs in Endocrine Society (ES) and AACE guidelines but both include patients with a T-score at or below -2.5 and

a history of fracture, or a history of multiple fractures. [8 11] An additional definition of very high risk in the AACE guidelines includes patients with a T-score at or below -3.0, regardless of fracture history. [8]

- The goal of therapy is to decrease osteoporotic fractures. However, there is insufficient evidence that one anabolic bone medication is superior to another or that bisphosphonates should be stopped after a "treatment course" and therapy changed to a different mechanism of action.
    * The 2019 Endocrine Society Osteoporosis guidelines update, and Agency for Healthcare Research and Quality (AHRQ) concluded that continuation of bisphosphonates after a three-to-five-year treatment course reduces some measures of vertebral fractures in high-risk patients. [11 12]
    * Based on this data, the ES recommends continued treatment if the patient remains at high fracture risk (which include multiple spine fractures or hip/spine T-score < 2.5) after a three to five years of bisphosphonate therapy. However, the guideline does not specifically recommend switching mechanism of action for ongoing use beyond three to five years. [11] In addition, the guideline considers the risks associated with ongoing bisphosphonate therapy, such as ONJ, to outweigh the risks of stopping therapy in higher risk patients. [11]
    * Patients with low-moderate fracture risk may consider a drug holiday, which is defined as a period of time when no osteoporosis medications are given.

Clinical Efficacy

Tymlos (abaloparatide)

- The efficacy of Tymlos (abaloparatide) was demonstrated in a randomized controlled trial that compared Tymlos (abaloparatide) to placebo, as well as open-label teriparatide), for 18 months of treatment in postmenopausal women. Patients in the pivotal trial of Tymlos (abaloparatide) in postmenopausal osteoporosis were required to have a T-score ≤ -2.5 and had a mean age of 68.8 years at baseline. [5]
    * Tymlos (abaloparatide) decreased the absolute risk of new vertebral fractures by 3.6% compared to placebo. New vertebral fractures occurred in 0.58% of participants in the Tymlos (abaloparatide) group and in 4.22% of those in the placebo group. [3 5]
    * Although considered an exploratory endpoint, new vertebral fractures occurred in 0.84% of participants treated with teriparatide). [5]

Evenity (romosozumab)

- In clinical trials, Evenity (romosozumab) reduced the number of new vertebral fractures versus either placebo or alendronate alone in women with postmenopausal osteoporosis. [13 14]
- The efficacy and safety of Evenity (romosozumab) in reducing the risk of osteoporotic fractures in postmenopausal women has been confirmed by two large randomized controlled trials, one comparing Evenity (romosozumab) versus placebo for 12 months followed by each arm receiving sequential denosumab therapy for 12 months (FRAME) and the other comparing sequential therapy with Evenity (romosozumab) for 12 months followed by alendronate for 12 months versus 24 months of alendronate (ARCH). [13 14]

* At 24 months, new vertebral fractures occurred in 0.6% in the Evenity (romosozumab) group, as compared with 2.5% in the placebo group (representing a 75% lower risk with romosozumab). Though clinical fracture rates differed significantly at 12 months, it did not reach statistical significance at 24 months. [13]
* Over a period of 24 months, a 48% lower risk of new vertebral fractures was observed in the romosozumab-to-alendronate group than in the alendronate-to-alendronate group (6.2% vs 11.9%, respectively). At the time of the primary analysis, Evenity (romosozumab) followed by alendronate resulted in a 27% lower risk of clinical fracture and a 38% lower risk of hip fracture than alendronate alone. [14]
* There was one randomized-controlled trial comparing Evenity (romosozumab) versus teriparatide) in postmenopausal women and one comparing Evenity (romosozumab) versus placebo in osteoporotic men that showed improved bone mass density in the Evenity (romosozumab) group but the quality of evidence of both studies was poor and applicability was limited. [15]

Teriparatide

- The efficacy and safety of teriparatide in reducing the risk of osteoporotic fractures in postmenopausal women has been confirmed by large randomized controlled trials. Patients treated in the pivotal trial of teriparatide in postmenopausal osteoporosis had a mean T-score of –2.6, a mean of 2.3 vertebral fractures, and a mean age of 69.5 years at baseline. [6 16 17]
- Teriparatide has been shown to reduce the risk of vertebral and non-vertebral fractures; however, it is unknown if teriparatide protects against hip fracture. Teriparatide increases bone mineral density (BMD) in the spine but has little effect on BMD in the hip or forearm. [3]
- Patients on teriparatide in a head-to-head trial comparing teriparatide to risedronate had a smaller number of radiographic vertebral fractures 5.4% vs 12% and clinical fractures than the risedronate group. However, there were no differences in pain, height, and health-related quality of life measures. Most patients had at least one prior osteoporosis therapy (median duration of previous bisphosphonate use 3.6 years). [18]
- When treatment with teriparatide is discontinued, bone density quickly declines the following year, although fracture reduction may persist for one to two years. It appears that continued antiresorptive therapy is necessary to maintain gains in BMD after withdrawal of teriparatide . [6 7 19 20] Administration of alendronate following one year of teriparatide treatment has been shown to prevent this loss and in some cases will be associated with a further increase in BMD. Effect on fracture has not been evaluated. [21]
- Combination therapy using teriparatide and alendronate has not been shown to be more effective than monotherapy with either agent. [22]

Guidelines[1-3 11 23]

- Treatment for people at high risk for fracture is recommended by guidelines. [11] The definition of high risk includes:
  * A history of fracture of the hip or spine.

    * A bone mineral density in the osteoporosis range (T-score of -2.5 or lower).
    * A bone mineral density in the low bone mass or osteopenia range with a higher risk of fracture defined by a Fracture Risk Assessment Tool (FRAX) score for major osteoporotic fracture 10-year probability of 20% or higher OR Hip fracture 10-year probability 3% or higher.

- For patients who are at very high risk of fracture, initial therapy with denosumab or an anabolic agent may be considered. The Endocrine Society Guidelines define very high risk as those with severe osteoporosis (low T-score ≤ −2.5 and fractures) or multiple vertebral fractures.
- An injectable option [e.g., zoledronic acid, Prolia (denosumab), Evenity (romosozumab), Tymlos (abaloparatide), or teriparatide] is recommended for those with a prior fragility fracture or indicators of higher fracture risk (e.g., advanced age, frailty, glucocorticoids, very low T-scores, or increased fall risk); however, no one specific injectable option is preferred over another. [8 11] Of the treatment options, generic zoledronic acid is the lowest cost treatment choice.
- The World Health Organization (WHO) algorithm (FRAX) was developed to calculate the 10-yr probability of a hip fracture and the 10-yr probability of any major osteoporotic fracture (defined as vertebral, hip, forearm, or humerus fracture) considering femoral neck BMD and the clinical risk factors. The WHO algorithm pertains only to previously untreated patients. [2]
- 2019 Endocrine Society Osteoporosis guideline recommend initial treatment with bisphosphonates (alendronate, risedronate, zoledronic acid, and ibandronate). They are available at low cost and have a long history of use. Denosumab and anabolic bone medications are considered alternative initial treatments for patients who are not candidates for a bisphosphonate or who have not had an adequate response to bisphosphonates. [24]
- The 2019 Endocrine Society Osteoporosis guideline and American Society for Bone and Mineral Research (ASBMR) recommend post-menopausal osteoporotic (PMO) women be evaluated for fracture risk after three to five years of bisphosphonates. [11]
    * Patients with low-moderate fracture risk may consider a drug holiday, which is defined as a period when no osteoporosis medications are given.
    * For patients with high risk (which include multiple spine fractures or hip/spine T-score <-2.5) osteoporosis treatment should be continued, as the benefits likely outweigh potential harms. Guidelines do NOT specifically suggest changing mechanism of action, such as stopping a bisphosphonate and use of Prolia (denosumab) or an anabolic bone medication, such as Tymlos (abaloparatide), teriparatide , or Evenity (romosozumab).
- Endocrine Society guidelines also recommend dual-energy X-ray absorptiometry (DEXA) at the spine and hip every 1 to 3 years to assess the response to treatment. While there is uncertainty regarding what is considered an adequate response, guidelines state the stable or increasing BMD may indicate a good response. Switching treatments may also be considered in patients who experience a fracture. [11]

- There have not been adequate studies to evaluate the efficacy of switching to alternative therapies and the optimal duration of bisphosphonate therapy is unclear. However, sequential therapy with an antiresorptive agent (drug used to prevent further bone loss, such as a bisphosphonate) is recommended if continued treatment is warranted after completion of anabolic therapy.
- Preliminary data on sequential therapy in high risk patients suggests that initial treatment with an anabolic bone medication followed by an antiresorptive agent (bisphosphonate) may lead to better outcomes than the traditional antiresorptive agent followed then by the anabolic bone medication, however this data is varied, mostly based on small trials using bone density not fracture reduction, and is not supported by the Endocrine Society guidelines.[10 25]
    * The VERO trial, in which 65% of patients had previously been treated with bisphosphonates prior to receiving teriparatide, showed that the anti-fracture efficacy of teriparatide when compared to risedronate was similar regardless of the patient's prior treatment with bisphosphonates or not, with the effect being independent of the interval between prior bisphosphonate treatment and inclusion in the trial.

Investigational Uses

- Bone healing: There are no clinical trials to support the use of Tymlos (abaloparatide), Evenity (romosozumab), or teriparatide for bone healing. Although there is promising animal data and a few published case reports, osteoanabolic agents have not been proven in published clinical trials to be effective or safe for fracture healing (these types of high-quality studies are “randomized,” “double-blinded,” and “controlled” and involve large treatment groups). There is no evidence to support the use of Tymlos (abaloparatide), Evenity (romosozumab) for any other indications, including for the prevention of postmenopausal osteoporosis, use in pre-menopausal osteoporosis or osteoporosis in men.
- Combination therapy: There is insufficient evidence to establish the safety and efficacy of combination of anabolic bone medications [including Prolia (denosumab)] or use of anabolic bone medications after completion of a course of therapy.
    * The evidence for combination use is limited to one small trial in post-menopausal women (n=94) on teriparatide with denosumab. Although the combination resulted in a larger increase in BMD than either agent alone, the effect on fractures is unknown (no data). [26 27]
    * Combination therapy substantially raises the cost and potential for side effects. Until the effect of combination therapy on fracture is better understood, AACE does not recommend concomitant use of these agents. [3 27]

Safety

Evenity (romosozumab)

- Unlike with other anabolic bone medications, there is a boxed warning for potential risk of major adverse cardiovascular events, including myocardial infarction, stroke, and cardiovascular death with Evenity (romosozumab). In a clinical trial comparing Evenity (romosozumab) to alendronate, patients in the Evenity (romosozumab) arm had a 1.3

times higher likelihood of a serious cardiovascular events than patients in the alendronate arm. Evenity (romosozumab) should not be initiated in patients who have had a myocardial infarction or stroke within the preceding year.

Teriparatide and Tymlos (abaloparatide)

- Due to the potential risk of osteosarcoma, cumulative use of Tymlos (abaloparatide) and teriparatide (Forteo, t teriparatide [600mcg/2.4 ml], and teriparatide [620mcg/2.48 ml]) for more than 2 years is not recommended.
- Tymlos (abaloparatide) or teriparatide (Forteo, teriparatide [600mcg/2.4 ml], and teriparatide [620mcg/2.48 ml]) should not be prescribed to patients at increased risk for osteosarcoma including those with Paget's disease of bone, patients with previous radiation therapy, and patients with bone metastases or skeletal malignancies.

Dosing

- Tymlos (abaloparatide) may be covered for up to 24-months, given as 80 mcg daily, the dose studied in clinical trials. The safety and efficacy of higher doses or durations longer than 24 months have not been established.
- Evenity (romosozumab) may be covered for up to 12-months, given as 210 mg every month, the dose studied in clinical trials. The safety and effectiveness of higher doses have not been established. In clinical trials, the efficacy of Evenity (romosozumab) waned after 12 months.
- Teriparatide (Forteo, teriparatide [600mcg/2.4 ml], and teriparatide [620mcg/2.48 ml]) may be covered for up to 24-months, given as 20 mcg daily, the dose studied in clinical trials. The safety and efficacy of higher doses or durations longer than 24 months have not been established.

Cross References
Bone Density Studies rad2, Medical Policy Manual, TRGMPM – Radiology
Prolia, denosumab, Medication Policy Manual, Policy No dru223
Site of Care Review, Medication Policy Manual, Policy No. dru408
Xgeva, denosumab, Medication Policy Manual, Policy No dru393

Codes	**Number**	**Description**
HCPCS	J3111	Injection, romosozumab-aqqg (Evenity), 1mg

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Revision History

Revision Date	Revision Summary
9/19/2024	• Added additional criterion to define "very high risk" patients (T score ≤ - 3.0). • Added step therapy with generic teriparatide (600mcg/2.4ml) AND Tymlos (abaloparatide) for brand name Forteo (teriparatide) and teriparatide (620mcg/2.48ml) coverage.
3/24/2024	Added quantity limit criteria to COT language.
9/14/2023	Updated position statement regarding sequential therapy. No change to criteria. Removed "Bonsity" branding from policy. Teriparatide is no longer marketed under this name.
3/16/2023	Removed postmenopausal criterion from Tymlos (abaloparatide) to allow for coverage of new indication in males.
9/23/2022	• Reworded criteria for operational clarity (no change to intent). • Updated Bonsity to Teriparatide. • Clarified Teriparatide criteria a. AND b. must be met (no change to intent).
10/15/2021	• Reformatted Section B of policy coverage criteria to list each product separately. • Updated criteria to bypass step therapy requirements for patients at very high risk of fracture (T-score at or below -2.5 and a history of fragility fractures, or multiple fragility fractures).
4/21/2021	Updated not medically necessary uses to include requests for dosing higher that those listed in Table 1. No change to intent.
10/28/2020	• Added COT criteria. • Revised definition of ineffectiveness for bisphosphonates.
10/23/2019	• New combination policy replacing individual medication coverage policies for Tymlos (dru514), Forteo (dru085), and Evenity (dru594). Added new teriparatide product (Bonsity) to policy (effective 1/1/2020). • Limits coverage of Tymlos and Evenity to postmenopausal osteoporosis when alternative treatment options are not effective, the setting in which they were studied and have labeled indications. • Forteo and Bonsity are limited to osteoporosis OR patients at high risk for osteoporosis, when alternative treatments are not effective.

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Medication Policy Manual | **Policy No:** dru616

Topic: Zilretta, triamcinolone acetonide extended-release (ER) injectable suspension | **Date of Origin:** May 1, 2020

Committee Approval Date: September 19, 2024 | **Next Review Date:** 2025

Effective Date: December 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Zilretta (triamcinolone acetonide extended-release [ER] injectable suspension) is a steroid that is injected directly into the knee joint to help improve pain associated with osteoarthritis of the knee.

Policy/Criteria

I. Continuation of therapy (COT): Zilretta (triamcinolone acetonide ER) may be considered medically necessary for COT when full policy criteria below are met.

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

New starts (treatment-naïve patients):

II. Zilretta (triamcinolone acetonide ER) is considered not medically necessary for osteoarthritis of the knee.

III. Zilretta (triamcinolone acetonide ER) is considered investigational when used for all other conditions, including but not limited to:

A. Rheumatoid arthritis.
B. Osteoarthritis in joints other than the knee.

Position Statement

Summary

- Zilretta (triamcinolone acetonide extended-release [ER]) is an intra-articular corticosteroid, injected directly into the knee joint, and has been studied and approved to reduce the pain associated with osteoarthritis (OA) of the knee.
- The intent of the policy is to offer members the best value IA steroids for OA of the knee.
- There is no evidence that Zilretta (triamcinolone acetonide ER) is safer or more effective than generic IA steroids, such as triamcinolone acetonide immediate-release (IR) (generic Kenalog) for osteoarthritis. However, Zilretta (triamcinolone acetonide ER) is significantly more costly than various generic IA steroids (including methylprednisolone and triamcinolone IR). Therefore, the use of Zilretta (triamcinolone acetonide ER) for OA of the knee is considered not medically necessary.
- IA steroids are used for various other indications, such as rheumatoid arthritis, synovitis, or OA in other joints (such as the knee or shoulder). However, there are no trials of Zilretta (triamcinolone acetonide ER) in any other conditions. Therefore, the use of Zilretta (triamcinolone acetonide ER) in any condition other than OA of the knee is considered investigational.
- All IA steroids have steroid-related adverse events due to their mechanism of action. Intraarticular steroid use may increase risks of post-injection flares, skin or fat changes, cartilage damage, and transient increase in blood glucose. [1]
- There is interest in the use of Zilretta (triamcinolone acetonide ER) for patients with concomitant diabetes and osteoarthritis of the knee. However, there is inclusive evidence

that Zilretta (triamcinolone acetonide ER) is safer than other available triamcinolone acetonide formulations. [2 3] Increases in blood glucose are transient. Therefore, the use of Zilretta (triamcinolone acetonide ER) for patients with diabetes is not medically necessary.

Clinical Efficacy [1 2]

- The evidence supporting efficacy of Zilretta (triamcinolone acetonide ER) for improving pain associated with OA of the knee is based primarily on one pivotal randomized control trial that compared one injection of Zilretta (triamcinolone acetonide ER) to placebo or triamcinolone IR.
    * After 12 weeks, there was a marginal improvement in average daily pain (ADP) score with patients who received Zilretta (triamcinolone acetonide ER) versus those who received placebo.
    * Zilretta (triamcinolone acetonide ER) showed no added benefit over triamcinolone IR for OA of the knee.
- Although the American Association of Orthopaedic Surgeons (AAOS)[4] implies triamcinolone ER can be used over IR to improve patient outcomes, in the pivotal trial triamcinolone ER showed a numerical advantage but failed to show statistical significance at Week 12 in the weekly mean average daily pain (ADP) score compared to triamcinolone IR. Other evidence to support the use of ER over IR is based on a post-hoc subpopulation analysis. [5]

Investigational Uses

- There are no large, randomized-controlled published clinical trials evaluating the safety or efficacy of Zilretta (triamcinolone acetonide ER) for the treatment of rheumatoid arthritis or in any other indications aside from OA of the knee.

Safety

- There is no evidence that Zilretta (triamcinolone acetonide ER) is safer than triamcinolone immediate-release.
- Overall adverse event rates were comparable in the Zilretta (triamcinolone acetonide ER) and the triamcinolone IR arms of the pivotal efficacy study but the incidence of arthralgia and worsening of knee pain were higher in the Zilretta (triamcinolone acetonide ER) arm. Diabetics with uncontrolled blood sugars were excluded from the study. [2]
- Evidence for use in diabetic patients is limited to a single, small (N=33) parallel group study [3] comparing use of Zilretta (triamcinolone acetonide ER) versus triamcinolone acetonide immediate-release in diabetic patients with OA of the knee. These patients were on one to two oral medications and not managed on injectables; they had a hemoglobin A1c level of 6.5 to 9.0% at baseline.

Codes	Number	Description
HCPCS	J3304	Injection, triamcinolone acetonide (Zilretta), preservative free, extended-release, microsphere formulation, 1 mg

References

1. Zilretta- triamcinolone acetonide extended-release injectable suspension. Burlington, MA: Flexion Therapeutics, Inc.; May 2018
2. Conaghan PG, Hunter DJ, Cohen SB, et al. Effects of a Single Intra-Articular Injection of a Microsphere Formulation of Triamcinolone Acetonide on Knee Osteoarthritis Pain: A Double-Blinded, Randomized, Placebo-Controlled, Multinational Study. *J Bone Joint Surg Am*. 2018;100:666-77. PMID: 29664853
3. Russell SJ, Sala R, Conaghan PG, et al. Triamcinolone acetonide extended-release in patients with osteoarthritis and type 2 diabetes: a randomized, phase 2 study. *Rheumatology (Oxford)*. 2018;57:2235-41. PMID: 30203101
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5. Langworthy MJ, Conaghan PG, Ruane JJ, et al. Efficacy of Triamcinolone Acetonide Extended-Release in Participants with Unilateral Knee Osteoarthritis: A Post Hoc Analysis. *Adv Ther*. 2019;36(6):1398-411. PMID: 30968336

Revision History

Revision Date	Revision Summary
9/19/2024	No criteria changes with this annual review.
9/14/2023	No criteria changes with this annual review.
9/23/2022	Osteoarthritis in joints other than the knee was added as investigational.
10/15/2021	No criteria changes with this annual update.
10/28/2020	No criteria changes with this annual update.
6/3/2020	Corrected Date of Origin.
1/22/2020	New policy (effective 05/01/2020). Considered not medically necessary for osteoarthritis of the knee and investigational for all other indications. No evidence of efficacy and safety versus triamcinolone immediate-release.

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Medication Policy Manual

Policy No: dru620

Topic: Products with Therapeutically Equivalent Biosimilars/Reference Products:

- Bevacizumab
- Infliximab
- Long-acting Colony Stimulating Factors
- Rituximab
- Trastuzumab

Date of Origin: July 1, 2020

Committee Approval Date: December 12, 2024

Next Review Date: 2025

Effective Date: January 15, 2025

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

A biosimilar is a type of biologic drug that is highly similar to it an FDA-approved biologic drug, known as the reference product. Biosimilars provide equivalent clinical benefit to the original reference product ("therapeutically equivalent").

PLEASE NOTE: This policy and the coverage criteria below do not apply to preferred brands of bevacizumab, long-acting colony stimulating factors, rituximab, and trastuzumab (as listed in *Table 1*) as they do not require pre-authorization; however, all brands of infliximab are subject to Site of Care review.

Policy/Criteria

I. Continuation of therapy (COT) **and** new starts: The use of Zymfentra (infliximab-dyyb) subcutaneous is considered not medically necessary (see *Table 1*).

II. Continuation of therapy (COT): Non-preferred products (as listed in *Table 1*) may be considered medically necessary for COT when full policy criteria below are met, including Site of Care administration requirements (see below).

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

III. New starts (treatment-naïve patients): Non-preferred products (as listed in *Table 1*) may be considered medically necessary when criteria A and B below are met:

A. One of the following criteria 1, 2, or 3 below is met:

1. There is a documented intolerance or contraindication to all preferred product(s) (as listed in *Table 1*).

OR

2. **For infliximab non-preferred products only:** There is a documented loss of effectiveness with use of all of the preferred infliximab products (as listed in *Table 1*), defined as clinical documentation of **both** of the following (a and b):

a. The patient was clinically stable on the requested non-preferred infliximab product PRIOR to changing to the preferred infliximab products.

AND

b. An adequate trial of all of the preferred infliximab products was ineffective, defined as worsening or return of underlying disease symptoms while using the preferred brands of infliximab as compared to disease control while using the non-preferred brand of infliximab.

OR

3. **For Neulasta Onpro or Udenyca On-Body (pegfilgrastim pre-filled autoinjector device) only:** There is a documented medical need for the autoinjector device as established by meeting criteria a and b below.

a. Patient or patient's caregiver is not able to self-administer any of the pegfilgrastim PFS products (as listed in *Table 1*) due to significant behavioral issues, physical difficulties, and/or cognitive impairment including, but not limited to, those associated with developmental delay, down syndrome, dementia, or excessive anxiety such as severe needle phobia.

AND

b. Patient lives greater than 10 miles from the provider's office, such that it is not possible to return for administration of any of the pegfilgrastim PFS products (as listed in *Table 1*).

AND

B. For infliximab only (all products): Site of care administration requirements are met [refer to Medication Policy Manual, Site of Care Review, dru408].

Table 1: Products with Therapeutically Equivalent Biosimilars/Reference Products

	Product Name	Formulary Status
Bevacizumab Products		
Reference Product	Avastin (bevacizumab)	Non-preferred/PA required
Biosimilars	Alymsys (bevacizumab-maly)	Non-preferred/PA required
	Avzivi (bevacizumab-tnjn)	Non-preferred/PA required
	MVASI (bevacizumab-awwb)	**Preferred/No PA required** [a]
	Vegzelma (bevacizumab-adcd)	Non-preferred/PA required
	Zirabev (bevacizumab-bvzr)	**Preferred/No PA required** [a]
Infliximab Products		
Reference Product [b]	Remicade (infliximab)	Non-preferred/PA required
Intravenous (IV) Biosimilars [b]	Inflectra (infliximab-dyyb)	**Preferred/PA required** [b]
	infliximab (Janssen)	Non-preferred/PA required
	Renflexis (infliximab-abda)	Non-preferred/PA required
	Ixifi (infliximab-qbtx)	Non-preferred/PA required
	Avsola (infliximab-axxq)	**Preferred/PA required** [b]
Subcutaneous (SC) infliximab	Zymfentra (infliximab-dyyb)	Not medically necessary
Long-acting Colony Stimulating Factors		
Reference Product	Neulasta PFS (pegfilgrastim) Neulasta Onpro (pegfilgrastim)	Non-preferred/PA required
Biosimilars	Fulphila (pegfilgrastim-jmdb)	**Preferred/No PA required** [a]
	Fylnetra (pegfilgrastim-pbbk)	Non-preferred/PA required
	Nyvepria (pegfilgrastim-apgf)	**Preferred/No PA required** [a]
	Stimufend (pegfilgrastim-fpgk)	Non-preferred/PA required
	Udenyca (pegfilgrastim-cbqv)	Non-preferred/PA required
	Udenyca On-Body (pegfilgrastim-cbqv)	Non-preferred/PA required
	Ziextenzo (pegfilgrastim-bmez)	Non-preferred/PA required
Recombinant G-CSF	Rolvedon (eflapegrastim-xnst)	Non-preferred/PA required
	Ryzneuta (efbemalenograstim alfa-vuxw)	Non-preferred/PA required
Rituximab Products		
Reference Product	Rituxan (rituximab) Rituxan Hycela (rituximab SC)	Non-preferred/PA required
Biosimilars	Riabni (rituximab-arrx)	Non-preferred/PA required
	Ruxience (rituximab-pvvr)	**Preferred/No PA required** [a]
	Truxima (rituximab-abbs)	**Preferred/No PA required** [a]

	Product Name	Formulary Status
Trastuzumab Products		
Reference Product	Herceptin (trastuzumab) Herceptin Hylecta (trastuzumab SC)	Non-preferred/PA required
Biosimilars	Hercessi (trastuzumab-strf)	Non-preferred/PA required
	Herzuma (trastuzumab-pkrb)	Non-preferred/PA required
	Kanjinti (trastuzumab-anns)	**Preferred/No PA required** [a]
	Ogivri (trastuzumab-dkst)	Non-preferred/PA required
	Ontruzant (trastuzumab-dttb)	Non-preferred/PA required
	Trazimera (trastuzumab-qyyp)	**Preferred/No PA required** [a]

[a] Specified preferred products are not subject to pre-authorization (PA).

[b] All IV infliximab products are subject to Site of Care criteria review.

IV. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers the following products coverable only under the medical benefit (as provider-administered medications).

1. Bevacizumab

2. Rituximab

3. Trastuzumab

4. Infliximab intravenous (IV)

B. Pharmacy Services considers infliximab subcutaneous (SC) coverable under the pharmacy benefit (as self-administered medications).

C. Pharmacy Services considers all the pegfilgrastim pre-filled syringe (PFS) and recombinant G-CSF products coverable under the pharmacy benefit (as self-administered medications) OR coverable under the medical benefit (as provider-administered medications).

D. Pharmacy Services considers pegfilgrastim autoinjector devices (Neulasta Onpro and Udenyca On-Body) coverable only under the medical benefit (as a provider-administered medication).

E. When pre-authorization for **infliximab IV** is approved, the following quantity limitations will apply: Up to 14 infusions in a 12-month period the first year, then up to 13 infusions annually thereafter.

F. When infliximab SC is approved, the following quantity limitations will apply: Up to 26 doses (26-120 mg syringes/pens) in a 12-month period.

G. Authorization **may** be reviewed at least every 6 months. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

V. The use of Zymfentra (infliximab-dyyb) subcutaneous is considered not medically necessary.

Position Statement

Summary

- The intent of this policy is to cover non-preferred products only when preferred products are not a treatment option. In addition, the use of significantly more expensive formulations is considered "not medically necessary," and therefore not coverable (see *Table 1*).
- FDA-approved biosimilar medications are clinically not meaningfully different than their reference products, also called "therapeutically equivalent." Although small differences in clinically inactive portions of the molecule may exist, the FDA approval certifies that the manufacturer has shown their product to be identical in function. [1] There is no scientific basis to prefer one FDA-approved product over another; given similar efficacy and safety, most contracts consider more costly products not medically necessary.
- While eflapegrastim-xnst (Rolvedon) and efbemalenograstim alfa-vuwx (Ryzneuta) are not "therapeutically equivalent" or a biosimilar to pegfilgrastim, it may be considered therapeutically similar to pegfilgrastim. For the purposes of this policy, eflapegrastim-xnst (Rolvedon) and efbemalenograstim alfa-vuwx (Ryzneuta) are classified with other pegfilgrastim biosimilars.
- While Zymfentra (infliximab-dyyb) is not a biosimilar to Remicade, it may be considered therapeutically similar to infliximab. For the purposes of this policy, (infliximab-dyyb) (Zymfentra) is classified with other infliximab biosimilars.
- FDA-approved biosimilars offer a less costly alternative that is just as effective as the reference product.
    * There is no evidence that any one bevacizumab, infliximab, pegfilgrastim, rituximab, or trastuzumab product is safer or more effective than another, including subcutaneous (SC) products versus intravenous (IV) products.
    * **Preferred products:** Among these products, currently the preferred products (as listed in *Table 1*) provide the best value for health plan members.
    * **Non-preferred products:** Products NOT listed as "preferred," whether biosimilars and/or reference products, are considered non-preferred and not coverable, unless coverage criteria are met (as listed in *Table 1*). Although biosimilars offer a lower overall cost for care, the pricing between individual products is variable and the lowest net cost products are available for coverage.
    * **Not medically necessary products:** Products NOT listed as "preferred" or "non-preferred" are considered not medically necessary, and therefore not coverable. Pricing between individual products is variable and the lowest net cost products are available for coverage.
- For cancer indications: National guidelines published by NCCN have endorsed FDA-approved biosimilars as appropriate for all relevant indications. [2] The available peer reviewed data has demonstrated that FDA-approved biosimilars are not meaningfully different from reference products in terms of efficacy, safety, or immunogenicity.

- For Clinical trials: Coverage of services for members enrolled in clinical trials is provided consistent with current standards of care. FDA-approved biosimilars are not clinically different from reference products. Biosimilars are the current standard of care and have been endorsed by national guidelines such as NCCN. Reference products which are more costly than preferred biosimilars may be provided by study sponsors.
- Hospitals and health-systems have medication formularies developed independent of the health plan. The health plan is unable to cover more expensive products for the convenience of the hospital, health-system, provider, or member. Preferred biosimilar products represent the lowest cost to members and the health plan; the use of more expensive products without evidence of superior efficacy or safety is not medically necessary per the member's contract.

Infliximab intravenous (IV) and subcutaneous (SC) formulations

- There are several available biosimilars to Remicade (infliximab) (as listed in *Table 1*).
- Infliximab has been used to treat a variety of inflammatory conditions.
- Inflectra (infliximab-dyyb) and Avsola (infliximab-axxq), the health plan preferred brands of infliximab, has the same FDA-approved indications as Remicade (infliximab). However, the intent of this policy is to provide coverage for the best value infliximab product for health plan members, independent of indication of use. Significantly more expensive formulations are considered "not medically necessary," and therefore not coverable (see *Table 1*).
- Infliximab IV is coverable for up to 14 infusions in a 12-month period in the first year, based on a usual induction regimen of 5 mg/kg at weeks 0, 2 and 6 followed by a usual starting maintenance regimen of 5 mg/kg every 8 weeks thereafter, but may increase to 10 mg/kg up to every 4 weeks (up to 13 infusions per year). [3]
- If approved, infliximab SC is coverable for up to 26 doses (26-120 mg syringes/pens) in a 12-month period. If a higher dose beyond the quantity limit is required for disease remission, IV infliximab offers the most cost-effective infliximab option for members.

Pegfilgrastim

- There is no evidence that any one pegfilgrastim product is safer or more effective than another. Among these products, preferred PFS pegfilgrastim products provide the best value for members.
- The FDA reaffirmed the lack of superiority of one dosage form of pegfilgrastim over others. In July 2021, the FDA issued a warning to the manufacturer of Neulasta Onpro for misleading promotional material, based on an observational study. In short, the FDA determined claims of superiority of pegfilgrastim via the on-body injector Onpro over pegfilgrastim delivered through a prefilled syringe are not supported due to limitations of the available data. "The promotional communication's misleading claims and presentations could cause healthcare providers to conclude that pegfilgrastim delivered through the Onpro on-body injector is more effective than pegfilgrastim delivered through a prefilled syringe or that it is more effective than FDA-licensed biosimilar pegfilgrastim products, which are only delivered through a prefilled syringe."

- Like pegfilgrastim, eflapegrastim-xnst (Rolvedon) and efbemalenograstim alfa-vuwx (Ryzneuta) are types of granulocyte colony stimulating factors(G-CSF). They were produced by adding an Fc fragment to human G-CSF.[7-8] Efbemalenograstim alfa-vuwx (Ryzneuta) is a non-pegylated G-CSF product.[8]

Subcutaneous (SC) formulations: Rituxan Hycela and Herceptin Hylecta [2-6]

- Rituximab for IV infusion and trastuzumab for IV infusion, the "reference product" to the SC formulation, have been available for many years with proven efficacy and safety in their respective cancer indications and the preferred products do not require pre-authorization.
- Rituximab/hyaluronidase SC (Rituxan Hycela) and trastuzumab/hyaluronidase SC (Herceptin Hylecta) are subcutaneous formulations for injection under the skin with hyaluronidase. Hyaluronidase is used to facilitate a large volume SC injection and allows for a faster rate of dose administration (versus traditional SC infusion).
- Both these SC products were FDA-approved based on non-inferiority to the IV formulation in pharmacokinetic studies in patients with cancer [Rituxan Hycela in follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), and chronic lymphocytic leukemia (CLL) and Herceptin Hylecta in HER2+ breast cancer].
- The NCCN guidelines recognize trastuzumab IV, biosimilar, and trastuzumab/hyaluronidase SC (Herceptin Hylecta) as a treatment option for HER2-positive breast cancers where trastuzumab is recommended. Likewise, NCCN recognizes rituximab IV, biosimilar, and rituximab/hyaluronidase SC as a treatment option for various B-cell lymphomas, including follicular lymphoma, diffuse large B-cell lymphoma, and chronic lymphocytic leukemia, where rituximab is recommended.

Cross References
BlueCross BlueShield Association Medical Policy, 5.01.12; Trastuzumab [September 2024]
BlueCross Blue Shield Association Medical Policy, 5.01.15 Off Label Use of Infliximab [April 2024]
Site of Care Review, Medication Policy Manual, Policy No. dru408
Drugs for chronic inflammatory diseases, Medication Policy Manual, Policy No. dru444
Provider-administered drugs for chronic inflammatory diseases (for UMP plans), Medication Policy Manual, Policy No. dru900
BlueCross BlueShield Association Medical Policy, 5.01.24 Nononcologic Uses of Rituximab [November 2024]
BlueCross BlueShield Association Medical Policy, 2.03.05 – Uses of Monoclonal Antibodies for the Treatment of Non-Hodgkin Lymphoma [November 2024]

Codes	Number	Description
HCPCS	Q5126	Injection, bevacizumab-maly, biosimilar, (Alymsys), 10 mg
HCPCS	J9035	Injection, bevacizumab, (Avastin), 10 mg
HCPCS	Q5121	Injection, infliximab-axxq, biosimilar, (Avsola), 10 mg
HCPCS	Q5130	Injection, pegfilgrastim-pbbk, biosimilar, (Fylnetra), 0.5 mg
HCPCS	J9355	Injection, trastuzumab, excludes biosimilar, (Herceptin), 10 mg
HCPCS	J9356	Subcutaneous, trastuzumab, and hyaluronidase-oysk (Herceptin Hylecta), 10 mg
HCPCS	Q5113	Injection, trastuzumab-pkrb, biosimilar, (Herzuma), 10 mg
HCPCS	Q5103	Injection, infliximab-dyyb, biosimilar, (Inflectra), 10 mg
HCPCS	Q5109	Injection, infliximab-qbtx, biosimilar, (Ixifi), 10 mg
HCPCS	Q5117	Injection, trastuzumab-anns, biosimilar, (Kanjinti), 10 mg
HCPCS	Q5107	Injection, bevacizumab-awwb, biosimilar, (Mvasi), 10 mg
HCPCS	J2506	Injection, pegfilgrastim (Neulasta, Neulasta Onpro), excludes biosimilar, 0.5 mg
HCPCS	Q5122	Injection, pegfilgrastim-apgf, biosimilar, (Nyvepria), 0.5 mg
HCPCS	Q5114	Injection, trastuzumab-dkst, biosimilar, (Ogivri), 10 mg
HCPCS	Q5112	Injection, trastuzumab-dttb, biosimilar, (Ontruzant), 10 mg
HCPCS	J1745	Injection, infliximab, excludes biosimilar, (Remicade, Janssen Inflectra), 10 mg
HCPCS	Q5104	Injection, infliximab-abda, biosimilar, (Renflexis), 10 mg
HCPCS	Q5123	Injection, rituximab-arrx, biosimilar, (Riabni), 10 mg
HCPCS	J9312	Injection, rituximab, (Rituxan), 10 mg
HCPCS	J9311	Injection, rituximab 10 mg and hyaluronidase, (Rituxan Hycela SC)
HCPCS	J1449	Injection, eflapegrastim-xnst, (Rolvedon), 0.1mg
HCPCS	J9361	Injection, efbemalenograstim alfa-vuxw, biosimilar (Ryzneuta), 0.5mg
HCPCS	Q5127	Injection, pegfilgrastim-fpgk, biosimilar, (Stimufend), 0.5 mg
HCPCS	Q5115	Injection, rituximab-abbs, biosimilar, (Truxima), 10 mg
HCPCS	Q5111	Injection, pegfilgrastim-cbqv, biosimilar, (Udenyca, Udenyca On-body), 0.5 mg
HCPCS	Q5129	Injection, bevacizumab-adcd (Vegzelma), biosimilar, 10 mg

References

1. Biosimilar and Interchangeable Products. [cited 07/17/2024]; Available from: https://www.fda.gov/drugs/biosimilars/biosimilar-products-information
2. National Comprehensive Cancer Network (NCCN) Drugs & Biologics Compendium. 2020 [Updated periodically]. [cited 3/15/2022]; Available from: https://www.nccn.org/professionals/drug_compendium/content/
3. Facts and Comparisons. Online database [updated periodically]. Accessed 11/6/2023.
4. Rituxan Hycela (rituximab and hyaluronidase human) injection, for subcutaneous use [package insert]. South San Francisco, CA: Genentech, Inc.; June 2021
5. Herceptin Hylecta (trastuzumab and hyaluronidase human) injection, for subcutaneous use [package insert]. South San Francisco, CA: Genentech, Inc.; June 2024
6. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines (various) [Updated periodically]. [cited 3/15/2022]; Available from: https://www.nccn.org/guidelines/category_1
7. Eflapegrastim-xnst (Rolvedon) [package insert]. Irvine, CA: Spectrum Pharmaceuticals Inc; June 2023.
8. Efbemalenograstim alfa-vuwx (Ryzneuta) [package insert]. Evive Biotechnology Singapore Pte. Ltd. November 2023.

Revision History

Revision Date	Revision Summary
12/12/2024	Effective 1/15/25: • Updated Zymfentra (infliximab-dyyb) subcutaneous as not medically necessary.
9/19/2024	• Added newly FDA-approved Hercessi (trastuzumab-strf) to policy as non-preferred. • Added HCPCS code for Ryzneuta (efbemalenograstim alfa-vuwx).
3/21/2024	Added newly FDA-approved Ryzneuta (efbemalenograstim alfa-vuwx), Udenyca On-Body (pegfilgrastim-cbqv), and Avzivi (bevacizumab-tnjn) to policy as non-preferred.
12/7/2023	Added Zymfentra (infliximab-dyyb) as non-preferred infliximab product with quantity limitation (QL)
9/14/2023	Effective 1/1/24: Updated preferred products.
6/15/2023	No changes to criteria with this annual update.
12/9/2022	Effective 1/15/23: • Added newly FDA-approved Vegzelma (bevacizumab-adcd) to policy as non-preferred. • Moved pegfilgrastim products from dru563 to this policy. Updated step therapy requirements for Neulasta Onpro to bypass preferred product requirements if medical need requirements are met. No other change to intent. • Added newly FDA-approved Rolvedon (eflapegrastim-xnst) to policy as non-preferred.

Revision Date	Revision Summary
6/17/2022	• Added new bevacizumab product to policy as non-preferred: Alymsys (bevacizumab-maly). • Modified criteria wording, for operational clarity (no change to intent of the criteria with this annual update). • Reformatted product table, to delineate the preferred/non-preferred and reference product/biosimilar. • Removed Quantity Limits.
10/15/2021	• Retitled policy to "Products with Therapeutically Equivalent Biosimilars/Reference Products." • Added infliximab (Janssen) to policy as non-preferred.
8/25/2021	Added infliximab products to policy, including Site of Care requirements.
4/21/2021	• Added subcutaneous products to policy as non-preferred: Rituxan Hycela (rituximab, hyaluronidase), Herceptin Hylecta (trastuzumab, hyaluronidase-oysk). • Updated position statement.
1/20/2021	• Added new rituximab product to policy as non-preferred: Riabni (rituximab-arrx) • Updated position statement.
6/9/2020	Added HCPCS code for Ruxience (rituximab-pvvr).
4/22/2020	Added rituximab to policy.
1/22/2020	New policy (effective 7/1/2020). Limits coverage to patients who have an intolerance or contraindication to a preferred product.

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Medication Policy Manual

Policy No: dru621

Topic: Intravitreal Vascular Endothelial Growth Factor (VEGF) Inhibitors:

- aflibercept (Ahzantive, Enzeevu, Eylea, Eylea HD, Opuviz, Pavblu, Yesafili)
- Beovu, brolucizumab
- ranibizumab (Byooviz, Cimerli, Lucentis, Susvimo)
- Vabysmo, faricimab-svoa

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IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

The medications in this policy are all inhibitors of vascular endothelial growth factor (VEGF), which prevent the formation of new blood vessels. They are injected directly into the eye (intravitreal) to treat a variety of eye conditions, by reducing swelling (blood vessel leakage and inflammation). Susvimo is a newer formulation that delivers ranibizumab injection via ocular implant.

Policy/Criteria

Most contracts require pre-authorization approval of intravitreal vascular endothelial growth factor (VEGF) inhibitors (as listed in *Table 1*) prior to coverage.

I. Continuation of therapy (COT): Intravitreal vascular endothelial growth factor (VEGF) inhibitors may be considered medically necessary for COT when criterion A or B below is met.

A. Both of the following:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. **For Susvimo only:** Treatment with a lower-cost ranibizumab, Byooviz (ranibizumab-nuna), Cimerli (ranibizumab-eqrn) or Lucentis (ranibizumab), was ineffective, not tolerated, or use is contraindicated.

OR

B. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note: *Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Intravitreal VEGF inhibitors may be considered medically necessary when there is clinical documentation that step therapy requirements below are met:

A. Step therapy requirements are considered met when:

1. Treatment with the required product(s) (as listed in *Table 1*) was ineffective, not tolerated, or use is contraindicated.

OR

2. There is evidence in the patient's paid medical claim history that the patient has used the required product(s) (as listed in *Table 1*).

Table 1. Intravitreal VEGF Inhibitor Products

Product Group	Products	Step Therapy Requirements
Level 1	- bevacizumab	No PA required when used in the eye
Level 2	- Byooviz (ranibizumab-nuna) - Cimerli (ranibizumab-eqrn) - Lucentis (ranibizumab)	**1.** Treatment with a Level 1 product
Level 3	- Ahzantive (aflibercept-mrbb) - Beovu (brolucizumab-dbll) - Enzeevu (aflibercept-abzv) - Eylea (aflibercept) - Eylea HD (aflibercept) - Opuviz (aflibercept-yszy) - Pavblu (aflibercept-ayyh) - Yesafili (aflibercept-jbvf)	**1.** Treatment with a Level 1 product **AND** **2.** Treatment with a Level 2 product
Level 4	- Susvimo (ranibizumab injection via ocular implant) - Vabysmo (faricimab-svoa)	**1.** Treatment with a Level 1 product **AND** **2.** Treatment with a Level 2 product **AND** **3.** Treatment with a Level 3 product

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers intravitreal VEGF inhibitors coverable only under the medical benefit (as provider-administered medications).

B. Authorization **may** be reviewed annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

Position Statement

- The intent of this policy is to cover higher cost branded VEGF inhibitors when lower cost options (as listed in the coverage criteria) are ineffective or not a treatment option, as detailed in the coverage criteria.
- Bevacizumab is the lowest cost VEGF inhibitor for the treatment of ocular conditions and therefore does not require pre-authorization (PA) for ocular conditions.
- Although intravitreal VEGF inhibitors have different indications, they have demonstrated evidence of efficacy for maintaining or improving visual acuity across various retinal disorders in clinical trials.
- Intravitreal VEGF inhibitors all work using the same mechanism of action by binding to the receptor binding site of active forms of VEGF-A. Likely because of similarities in mechanism of action, studies have not been able to demonstrate that one product is significantly superior to another in efficacy or safety (as detailed in the *Clinical Efficacy* sections below, by diagnosis).
    * Recently approved Vabysmo (faricimab-svoa) works by inhibiting both VEGF-A and angiopoietin-2 (Ang-2). However, per the FDA labeling, the contribution of Ang-2 inhibition to treatment effect remains unknown at this time. [1]
    * Ranibizumab injection via ocular implant (Susvimo) is a long-acting formulation of ranibizumab. Susvimo consists of a small surgically implanted "port" that releases ranibizumab continually for up to six months, at which time the port is refilled. In clinical trials, ranibizumab injection via ocular implant (Susvimo) was non-inferior to ranibizumab intravitreal injection (Lucentis). However, there was a temporary drop in visual acuity and increase in ocular adverse events with ranibizumab injection via ocular implant (Susvimo).
- Byooviz (ranibizumab-nuna) and Cimerli (ranibizumab-eqrn) are FDA-approved biosimilars to Lucentis (ranibizumab). These biosimilars offer an equally effective alternative to the reference product, ranibizumab intravitreal injection (Lucentis), as well as lower cost than ranibizumab injection via ocular implant (Susvimo). FDA-approved biosimilar medications are clinically not meaningfully different than their reference products, also called "therapeutically equivalent." Although small differences in clinically inactive portions of the molecule may exist, the FDA approval certifies that the manufacturer has shown their product to be identical in function. There is no scientific basis to clinically prefer one FDA-approved product over another; given similar efficacy and safety, most contracts consider more costly products not medically necessary.
- Evidence-based recommendations and clinical guidelines do not differentiate the VEGF inhibitors in clinical practice recommendations. Evidence-based recommendations and clinical guidelines equally recommend the use of VEGF inhibitors, including bevacizumab, for the treatment of neovascular (wet) age-related macular degeneration (wAMD), macular edema secondary to retinal vein occlusion (RVO), retinopathy of prematurity (ROP), and diabetic macular edema (DME; including diabetic retinopathy associated with DME).

- Despite the availability of well-designed studies that have shown similar efficacy between VEGF inhibitors, there is an absence of studies and evidence-based guidelines to guide treatment in refractory AMD individuals who have failed one or more VEGF inhibitors, due to lack of or incomplete response. Defining non-responders to treatment is an additional challenge among clinicians given that there is no universally accepted nomenclature for describing different types of non-responsiveness. Multiple clinical features are used in practice as measures of treatment efficacy and response (improvement in visual acuity, reduction in intraretinal or subretinal fluid, increase in central macular thickness etc.); patients without a particular response may or may not be deemed as non-responders depending on provider approach.
- In clinical practice, approaches to subsequent treatment for refractory AMD individuals include reducing treatment intervals, increasing the dose of the current treatment if available, or switching to a different medication.
- Higher-cost VEGF products, including Eylea / Eylea HD (aflibercept)have been studied in other vascular-related ocular conditions. The clinical benefit of higher-cost VEGF products in these indications is uncertain to date.
- Previous concerns over the use of compounded or repackaged products, such as bevacizumab, have been alleviated by the FDA's 2013 Drug Quality and Security Act, which provides better oversight of compounding pharmacies. In addition, the American Society of Retina Specialists has published online safety information about compounding pharmacies to help retina specialists choose high-quality providers of bevacizumab. Furthermore, in February 2015 the FDA issued Draft Guidance regarding drug compounding and repackaging of biologics to further standardize quality of bevacizumab. [2-4]

Clinical Efficacy

Neovascular (wet) Age-related Macular Degeneration (AMD)

- Intravitreal VEGF inhibitors have similar effectiveness for wet AMD. They all have been shown to maintain or improve vision based clinical trials. Systematic reviews have concluded that the comparators have similar efficacy.
    * One high-quality systematic review of Avastin (bevacizumab) in the treatment of wAMD concluded that it improves visual acuity and central retinal thickness (moderate correlate to visual acuity) and is more effective than photodynamic therapy (without verteporfin). [5]
    * A 2019 systematic review of VEGF inhibitors in wAMD concluded that there were no major differences with respect to vision related outcomes comparing Lucentis (ranibizumab) and Avastin (bevacizumab) after one year of treatment. Of note, the review did not include any trials with Eylea (aflibercept) or Beovu (brolucizumab-dbll). [6]
    * A 2016 systematic review focusing on Eylea (aflibercept) concluded that intravitreal aflibercept has similar efficacy to Lucentis (ranibizumab) in terms of improvement and stability in visual acuity after one and two years of treatment. [7]

    * Beovu (brolucizumab-dbll) was evaluated in two phase 3 randomized, controlled trials: HAWK and HARRIER. Both studies had nearly identical designs and endpoints. Results demonstrated the brolucizumab was non-inferior to aflibercept for maintaining visual acuity. [8]

- The American Academy of Ophthalmology (AAO) guidelines state that in patients with wAMD, intravitreal injection therapy using VEGF inhibitors are the most effective way to manage wAMD and represents the first line of treatment. Guidelines include Eylea (aflibercept), Avastin (bevacizumab), Lucentis (ranibizumab), and Beovu (brolucizumab-dbll) for the treatment of wet AMD. The AAO does not recommend the use of Macugen (pegaptanib) in the treatment of wAMD due to evidence indicating that it does not improve visual acuity on average in patients with new onset wAMD unlike other currently available VEGF inhibitors. [9] The guidelines have not been updated since the approval of newer VEGF products, such as Vabysmo (faricimab-svoa).

Diabetic Macular Edema (DME)

- There is moderate certainty that VEGF inhibitors improve visual acuity in patients with DME; however, there is insufficient evidence to demonstrate that one VEGF inhibitor is clinically superior to another in the treatment of DME based on one high-quality systematic review and one government-sponsored comparative study.
    * A Cochrane systematic review (2018) concluded that Eylea (aflibercept), Avastin (bevacizumab), and Lucentis (ranibizumab) are more effective than laser photocoagulation in improving visual acuity (i.e., likelihood of gaining three or more lines of vision). Although there were no significant sub-group differences in visual acuity between the VEGF inhibitors, there was insufficient power to detect a difference between them. [10]
    * A government-sponsored trial (PROTOCOL T) evaluated mean improvement in visual acuity for up to two years in patients with DME treated in a randomized fashion 1:1:1, with Eylea (aflibercept) 2mg, Avastin (bevacizumab) 1.25mg or Lucentis (ranibizumab) 0.3mg, every 4 weeks: [11 12]
        - The trial concluded that there was no clinically meaningful difference in improvement in visual acuity in the overall DME population.
        - It was noted that Eylea (aflibercept) was modestly more effective (approximate mean improvement of 6 letters) at improving visual acuity relative to the other VEGF inhibitors in a subset of patients with lower baseline visual acuity at the 1- and 2-year follow-up; however, there was low confidence in the trial results due to an imbalance in concomitant treatment between study arms, potential for bias as investigators were not blinded to treatment, and that results may not apply to eyes with persistent or recurrent DME that are already being treated with anti-VEGF inhibitors, based on study eligibility criteria.
- More recently, a new formulation of Susvimo (ranibizumab) was approved for delivery of ranibizumab injection via an implanted port. Clinical trials of ranibizumab via ocular implant (Susvimo) demonstrated comparable efficacy results to ranibizumab intravitreal injections (Lucentis); however, the implant was associated with a higher incidence of

adverse events, including a 3-fold higher rate of endophthalmitis. The clinical efficacy and safety of ranibizumab via ocular implant (Susvimo) was assessed in one randomized, visual assessor-masked, non-inferiority trial (Archway; n=415). [13]

* Patients diagnosed with wAMD within the nine months prior to screening and received at least three doses of intravitreal VEGF inhibitors. Only VEGF responders were included in the trial.
* Patients were randomized to ranibizumab via ocular implant (Susvimo) with refills every 24 weeks or ranibizumab intravitreal injections (Lucentis) every 4 weeks.
* The primary efficacy endpoint was the change from baseline in best-corrected visual acuity (BCVA) score averaged over week 36 and 40.
* Efficacy of ranibizumab via ocular implant (Susvimo) was noninferior to ranibizumab intravitreal injections (Lucentis) with a change from baseline BCVA of +0.2 and +0.5, respectively at 36-40 weeks [difference of -0.3 (CI -1.7 to 1.1) meeting non-inferiority].
* However, the trial was relatively short, given the chronic progressive nature of wAMD. Therefore, the durability of the treatment effect is unknown.
* Of note, patients treated with the ranibizumab via ocular implant (Susvimo) experienced a transient and reversible postsurgical drop in visual acuity, as measured by Early Treatment Diabetic Retinopathy Study Letters (ETDRS), after implant insertion, with vision returning to baseline by week 8.
* In addition, safety concerns inherent to an ocular implant may limit the utility of ranibizumab via ocular implant (Susvimo) (see *Safety* section below for additional details).

- The American Academy of Ophthalmology guidelines support the use of VEGF inhibitors, including Lucentis (ranibizumab), Eylea (aflibercept), and Avastin (bevacizumab) in the treatment of DME (including diabetic retinopathy associated with DME). [14 15]
  * AAO recommendations were based on trials comparing Eylea (aflibercept), Avastin (bevacizumab), and Lucentis (ranibizumab) to focal laser treatment (READ-2, BOLT, AND DA VINCI studies, respectively). All trials showed that treatment with VEGF inhibitors resulted in statistically and clinically significant improvements in visual acuity in patients with DME after one to two years of treatment compared to laser treatment.
  * In the BOLT study, Avastin (bevacizumab) was also shown to reduce the level of severity of diabetic retinopathy in patients with DME over the 12-month treatment period whereas the severity remained relatively stable in patients who received laser therapy. [16]
  * The guidelines have not been updated since the availability of newer VEGF products, such as ranibizumab injection via ocular implant (Susvimo), Vabysmo (faricimab-svoa), or the biosimilars.

Diabetic Retinopathy (without DME)

- Treatment with Lucentis (ranibizumab) demonstrated efficacy in the treatment of diabetic retinopathy without diabetic macular edema in the NIH-funded Diabetic Retinopathy Clinical Research Network Study. [17 18] The study compared Lucentis (ranibizumab) to panretinal laser therapy in patients with diabetic retinopathy, and found that patients both with and without diabetic macular edema had improved short-term and 2-year outcomes with Lucentis (ranibizumab) compared to panretinal or scatter photocoagulation laser therapy. [17]
- The American Academy of Ophthalmology guidelines support the use of VEGF inhibitors, including Lucentis (ranibizumab), Eylea (aflibercept), and Avastin (bevacizumab) in the treatment of DME (including diabetic retinopathy associated with DME). [14 15] [See *Diabetic Macular Edema* above, for details]
- Trials are ongoing for the use of Beovu (brolucizumab-dbll) in diabetic retinopathy. [19]

Retinal Vein Occlusion

- There is moderate certainty that VEGF inhibitors [Eylea (aflibercept), Avastin (bevacizumab), Macugen (pegaptanib), and Lucentis (ranibizumab)] are more effective than sham injection or laser therapy in maintaining or improving visual acuity in patients with macular edema secondary to RVO (branch and central; BRVO, CRVO) based on two Cochrane systematic reviews (2020); however, there is insufficient evidence to demonstrate that one VEGF inhibitor is clinically superior to another due to the lack of direct comparative evidence. [20 21]
- More recently, one non-inferiority LEAVO trial evaluated Lucentis (ranibizumab), Eylea (aflibercept), or bevacizumab in patients with CRVO (n = 463). [22] The pre-defined null hypothesis that Eylea (aflibercept) and bevacizumab are each inferior to Lucentis (ranibizumab), tested with a non-inferiority margin of –5 visual acuity letters over 100 weeks. The study demonstrated that Eylea (aflibercept) was non-inferior to Lucentis (ranibizumab), but not superior. However, the study was unable to demonstrate non-inferiority of bevacizumab to Lucentis (ranibizumab). Therefore, the aforementioned conclusion remains unchanged: there is insufficient evidence to demonstrate that one VEGF inhibitor is clinically superior to another due to the lack of direct comparative evidence.
- Results from two randomized, multicenter, phase III trials (BALATON and COMINO) demonstrated monthly treatment with Vabysmo (faricimab-svoa) provided early and sustained improvement in vision in individuals with branch and central RVO, meeting the primary endpoint of non-inferior visual acuity gains at 24 weeks, compared to Eylea (aflibercept). The BCVA gains from baseline at week 24 with Vabysmo (faricimab-svoa) were noninferior to Eylea (aflibercept) in BALATON (adjusted mean [95% confidence interval] change: +16.9 letters [15.7, 18.1] vs. +17.5 letters [16.3, 18.6]) and COMINO (+16.9 letters [15.4, 18.3] vs. +17.3 letters [15.9, 18.8]). [23]
- Evidence-based recommendations from UpToDate, the American Academy of Ophthalmology, and the Centers for Medicare and Medicaid Services support the use of VEGF inhibitors [Eylea (aflibercept), Avastin (bevacizumab), Lucentis (ranibizumab), and Vabysmo (faricimab-svoa)] for the treatment of macular edema secondary to retinal

vein occlusion. [24-26] As of publication of this policy, these recommendations have not been updated since the availability of newer VEGF products, such as ranibizumab injection via ocular implant (Susvimo), or the biosimilars.

Myopic Choroidal Neovascularization (mCNV)

- A Cochrane systematic review (2016) concluded that there is low-to-moderate certainty evidence for the efficacy of VEGF inhibitors to treat mCNV at one year and two years. [27] The authors also concluded that Lucentis (ranibizumab) and Avastin (bevacizumab) are equivalent in terms of efficacy in the treatment of patients with mCNV.
- Trials are ongoing for the use of Beovu (brolucizumab-dbll) in mCNV. [19]

Retinopathy of Prematurity (ROP)

- Retinopathy of prematurity (ROP) is a developmental vascular disorder that occurs in the retina of preterm infants and can lead to blindness. The incidence and severity of ROP increase with decreasing gestational age (GA) and birth weight. Severe ROP develops in approximately 40 percent of infants born at 22 to 25 weeks GA, 20 percent of those born at 25 to <27 weeks GA, and <5 percent of those born at 27 to 30 weeks GA. [42]
- Standard of care treatments for ROP include laser treatment and anti-VEGF injections including bevacizumab, ranibizumab, and aflibercept. [41]
- There is no evidence that any one anti-VEGF is safer or more effective than another for the treatment of ROP.

Refractory AMD

- Patients suffering from refractory or recurrent neovascular AMD (nAMD) may develop mechanisms of resistance to VEGF inhibitors which results in a diminished therapeutic effect. Most treatment approaches to refractory AMD are guided by provider clinical experience or preference, without specific guidelines available for this patient population.
- Evidence for treating refractory nAMD is limited to small, pilot studies or retrospective case reviews, not randomized controlled trials of significant size.
- The LAST study, a prospective pilot study of 9 subjects with subfoveal neovascular AMD with persistent subretinal or intraretinal fluid despite 6 months of treatment with either Lucentis (ranibizumab) 0.5mg/0.05ml or Avastin (bevacizumab) 1.25mg/0.05ml intravitreally, showed that at 6 months, high-dose Lucentis (ranibizumab) 2mg/0.05ml had the potential to maintain or improve visual acuity in patients with persistent fluid secondary to nAMD and despite prior monthly treatment with standard doses of VEGF-inhibitors. There was a mean improvement in visual acuity of 6 EDTRS letters; however, given the small sample size, it was not possible to make a statistical comparison between the two treatment groups. [28]

Other Uses

- The use of any VEGF inhibitor in conjunction with other VEGF inhibitors is considered investigational as there is no evidence evaluating the efficacy or safety of combination therapy.
- Trials of Eylea (aflibercept) in a variety of other conditions such as radiation retinopathy, central serous chorioretinopathy, and pathologic myopia are ongoing and are considered investigational due to lack of published, high-quality data.

- Published data evaluating Lucentis (ranibizumab) in several other conditions is preliminary. Larger well-controlled trials are needed to determine the clinical benefit of Lucentis (ranibizumab) in these conditions.
    * One study in 37 patients with retinal angiomatous proliferation evaluated Lucentis (ranibizumab) alone, and either Lucentis (ranibizumab) or intravitreal triamcinolone plus photodynamic therapy. Disease stabilization occurred in all three groups; however, a trend toward better visual acuity and anatomic restoration occurred in the triamcinolone/photodynamic therapy group. These results were confirmed at 3 years. [29 30]
    * A single-center pilot study in 10 patients with primary pterygia evaluated the tolerability of Lucentis (ranibizumab) either prior to surgery or at the time of surgery. [31]
    * A single-center pilot study in 10 patients undergoing trabeculectomy evaluated Lucentis (ranibizumab) to assist in wound healing when given with topical mitomycin C. [32]
    * Lucentis (ranibizumab) was evaluated versus photodynamic therapy in a single-center pilot study in 16 patients with chronic central serous chorioretinopathy. [33]

Safety [34]

- Intravitreal VEGF inhibitors have been associated with inflammation, blurred vision, corneal edema, eye discharge and irritation, and hypertension. However, a 2016 Cochrane review that concluded that neither Eylea (aflibercept) or Lucentis (ranibizumab) drug produces a greater incidence of systemic or vision-threatening complications. [7]
- Recent updates (2023) to prescribing information for Eylea/Eylea HD (aflibercept) and Vabysmo (faricimab-svoa) include warnings/precautions for the potential of retinal vasculitis with or without occlusion, based on post-marketing experience.
- Additional serious adverse effects reported with intravitreal VEGF inhibitors include endophthalmitis, retinal detachment, and iatrogenic traumatic cataract. After injection, patients should be advised to seek immediate care if the treated eye becomes red, painful, sensitive to light, or they notice a change in vision. There is no known difference between the safety profile of the currently available biosimilars and the innovator products.
- Although Lucentis (ranibizumab) has sufficient clinical safety experience, experience with the implant formulation of Susvimo (ranibizumab) is limited. In clinical trials, ranibizumab injection via ocular implant (Susvimo) was associated with a higher incidence of adverse events compared to monthly intravitreal injections of Lucentis (ranibizumab), including a three-fold higher rate of endophthalmitis, for which a black box warning is included in its prescribing information. In addition, the ranibizumab injection via ocular implant (Susvimo) and/or implant-related procedures have been associated with infection, hemorrhage, retinal detachment, implant dislocation, and decrease in visual acuity. [35]
- *Cardiovascular (CV) safety*: A meta-analysis evaluating the CV safety of intravitreal VEGF inhibitors in patients with wet AMD, DME, or RVO concluded that VEGF

inhibitors, specifically Avastin (bevacizumab) and Lucentis (ranibizumab), are not associated with a significant increase in risk of systemic CV and hemorrhagic events or in overall mortality, stroke, or CV mortality in elderly patients. However, the studies and meta-analysis were not sufficiently powered to correctly assess these risks. [36]

- *Comparative safety*: The trial conducted by the CATT research group comparing Lucentis (ranibizumab) to Avastin (bevacizumab) for the treatment of wet AMD found the following regarding safety: [17 18]
    * A statistically significant difference was seen at 52 weeks in the rates of serious systemic adverse events between the Lucentis (ranibizumab) and Avastin (bevacizumab) groups (19.0% vs 24.1%, P = 0.04).
    * A significant difference was also seen at 2 years [39.9% Avastin (bevacizumab) vs 31.7% Lucentis (ranibizumab); adjusted risk ratio 1.30; 95% CI: 1.07, 1.57; P = 0.009].
    * This difference was largely due to hospitalizations for infections such as pneumonia and urinary tract infections. It is uncertain if these events were related to either medication.
- *Compounded VEGF inhibitors* - Avastin (bevacizumab) is listed in national treatment guidelines and is recognized by the Centers for Medicare and Medicaid Services as a safe and effective treatment option for wet AMD, DME, and RVO. [12]
    * Avastin (bevacizumab), when used in the eye, must be extemporaneously compounded to achieve the appropriate dose. In 2011, a group of cases of endophthalmitis were reported with the use of Avastin (bevacizumab) which was determined to be the result of unsafe practices by one compounding pharmacy. [7 37 38]
    * While the use of Avastin (bevacizumab) continues to be associated with the risk of endophthalmitis, all intravitreal injections, including commercially available preparations of Eylea (aflibercept), Macugen (pegaptanib), and Lucentis (ranibizumab) carry this risk. [39 40]

Dosing [34]

- Eylea (aflibercept) 2 mg is injected intravitreally (into the eye) every 4 weeks for 12 weeks, then every 8 weeks. After one year of effective therapy patients may also be treated with one dose every 12 weeks. Eylea HD (aflibercept) 8 mg is injected intravitreally every 4 weeks (+/- 7 days) for the first three doses, followed by 8 mg every 8 to 16 weeks (+/- 1 week).
- Avastin (bevacizumab) 1.25 mg is injected intravitreally (into the eye) monthly or as needed.
- Beovu (brolucizumab) 6 mg is injected monthly for the first three doses, followed by 6 mg (one dose) every 8–12 weeks.
- Ranibizumab (biosimilars, Lucentis) 0.5 mg is injected intravitreally (into the eye) every 1 to 3 months.
- The Susvimo ocular implant system is initially inserted into the eye and the 2 mg ranibizumab injection solution refilled every 6 months.

- Vabysmo (faricimab-svoa) is injected monthly for the first four doses, followed by 6 mg (one dose) every 4-16 weeks, with significant variation in dosing dependent on indication and response to therapy.

Appendix 1: Nomenclature of ocular conditions treated with VEGF Inhibitors [24 41 42]

Diagnosis	Synonyms
Neovascular (wet) age-related macular degeneration	Exudative senile macular degeneration
	Age-related macular degeneration (ARMD)
	Choroidal neovascularization (CNV)
Diabetic Macular Edema and Diabetic Retinopathy	Diabetic macular edema (DME) associated with diabetic retinopathy
	DME due to Type 1 or Type 2 diabetic retinopathy
	DME due to nonproliferative or proliferative diabetic retinopathy (mild, moderate, or severe)
	Center involving diabetic macular edema
	Diabetic retinal edema
	Clinically significant diabetic macular edema (CSME)
Myopic choroidal neovascularization	Choroidal neovascularization secondary to pathologic myopia (mCNV)
	Pathologic myopia
Macular edema associated with Retinal Vein Occlusion	Macular edema associated with central retinal vein occlusion (CRVO)
	Macular edema associated with branch retinal vein occlusion (BRVO)
	Macular edema associated with tributary (branch) retinal vein occlusion

Codes	Number	Description
HCPCS	J0179	Injection, brolucizumab-dbll (Beovu), 1 mg
HCPCS	J0178	Injection, aflibercept (Eylea), 1 mg
HCPCS	J0177	Injection, aflibercept (Eylea HD), 8mg
HCPCS	J2778	Injection, ranibizumab (Lucentis), 0.1 mg
HCPCS	Q5128	Injection, ranibizumab-eqrn, biosimilar (Cimerli), 0.1mg
HCPCS	Q5124	Injection, ranibizumab-nuna, biosimilar, (Byooviz), 0.1 mg
HCPCS	J2779	Injection, ranibizumab, via intravitreal implant (Susvimo), 0.1 mg
HCPCS	J2777	Injection, faricimab-svoa (Vabysmo), 0.1 mg
HCPCS	J9035	Injection, bevacizumab, (Avastin) 10 mg
HCPCS	Q5107	Injection, bevacizumab-awwb, biosimilar, (Mvasi), 10 mg
HCPCS	Q5118	Injection, bevacizumab-bvzr, biosimilar, (Zirabev), 10 mg
HCPCS	Q5126	Injection, bevacizumab-maly, biosimilar (Alymsys), 10 mg
HCPCS	Q5129	Injection, bevacizumab-adcd biosimilar, (Vegzelma), 10 mg

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Revision History

Revision Date	Revision Summary
9/19/2024	• Added newly FDA-approved biosimilars Ahzantive (aflibercept-mrbb), Enzeevu (aflibercept-abzv) and Pavblu (aflibercept-ayyh) to Level 3. • Moved Lucentis (ranibizumab) from a Level 3 to Level 2 product. • Added HCPCS code for Cimerli (ranibizumab-eqrn).
6/20/2024	• Added newly FDA-approved biosimilars Opuviz (aflibercept-yszy) and Yesafili (aflibercept-jbvf) to policy. • HCPCS Appendix updated with new Eylea HD code (J0177).
3/21/2024	Removed 90-day lookback in criterion II.A.2 (certain agents have a 4-month dosing schedule or response to therapy may dictate an extended dosing schedule).
12/7/2023	Added Eylea HD, a new aflibercept higher dose product, to policy.
9/14/2023	No criteria changes with this annual review. Added information about retinopathy of prematurity (ROP) to backend of policy.
3/16/2023	No changes to criteria with this annual update.
9/23/2022	• Updated format of step therapy requirements for operational clarity. No change to intent. • Added Cimerli (ranibizumab-eqrn) to policy as a Level 2 product.

Revision Date	Revision Summary
3/18/2022	• Updated step therapy with lower-cost VEGFs (bevacizumab, biosimilars) to a claim look-back, for operational consistency. • Added step therapy with Lucentis (ranibizumab) to the ranibizumab injection via ocular implant (Susvimo) criteria. • Clarified name of formulation: ranibizumab injection via ocular implant (Susvimo). • Added Vabysmo (faricimab-svoa) per charter.
10/15/2021	Effective 1/1/2022: • Added newly FDA-approved biosimilar Byooviz (ranibizumab-nuna) to policy. • Updated step therapy criteria to require use of Byooviz (ranibizumab-nuna) prior to coverage of Eylea (aflibercept), Beovu (brolucizumab), or Lucentis (ranibizumab) in addition to bevacizumab. • Added Susvimo (ranibizumab) per charter.
4/21/2021	COT language added; no other changes to criteria with this annual update.
4/22/2020	No changes to criteria with this annual update.
1/22/2020	• New policy (effective 2/15/2020. Replaces individual drug coverage policies for Lucentis (ranibizumab) and Eylea (aflibercept). • Coverage criteria for Beovu (brolucizumab) have been added. • Limits use to those patients in which bevacizumab has been ineffective when used in the eye, unless contraindicated.

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Medication Policy Manual | **Policy No:** dru622

Topic: Padcev, enfortumab vedotin | **Date of Origin:** May 15, 2020

Committee Approval Date: June 20, 2024 | **Next Review Date:** 2025

Effective Date: July 15, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Padcev (enfortumab vedotin) is an antibody-drug conjugate that delivers chemotherapy to bladder cancer cells (cells that express nectin-4). It is given via intravenous infusion and is indicated for use in bladder cancer that has spread outside of the bladder.

Policy/Criteria

Most contracts require prior authorization approval of Padcev (enfortumab vedotin) prior to coverage.

I. Continuation of therapy (COT): Padcev (enfortumab vedotin) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Padcev (enfortumab vedotin) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A and B below are met.

A. A diagnosis of **locally advanced (unresectable) or metastatic urothelial carcinoma (bladder cancer).**

AND

B. Padcev (enfortumab vedotin) will be used in one of the following settings (1 or 2):

1. First-line in advanced disease setting: when the following criteria are met (a, b, c, and d):

a. The patient has not had prior systemic therapy (chemotherapy or immunotherapy) in the advanced disease setting (locally advanced or metastatic disease).

AND

b. The patient is ineligible for any platinum-containing chemotherapy (such as cisplatin or carboplatin).

PLEASE NOTE: Any platinum ineligibility may include poor kidney function (CrCl<60), poor performance status (≥2), significant hearing loss (≥ 25 dB), grade 2-4 peripheral neuropathy, heart failure, other comorbidities, etc.

AND

c. Padcev (enfortumab vedotin) will be used in combination with Keytruda (pembrolizumab).

AND

d. No prior therapy with PD-1/PD-L1 blocking antibody therapy (see *Appendix 1*).

OR

2. Subsequent line: The patient has relapsed or refractory disease and the following criteria are met (a and b):

a. Disease has progressed on or after each of the following prior therapies (i and ii):

i. A platinum-containing chemotherapy regimen (such as cisplatin, carboplatin), unless patient is ineligible for platinum-containing chemotherapy.

PLEASE NOTE: Use may have been in the neoadjuvant (before surgical resection)/adjuvant (after surgical resection), locally advanced, or metastatic settings]

AND

ii. Therapy with a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor (see *Appendix 1*) unless contraindicated or not tolerated.

AND

b. Padcev (enfortumab vedotin) will be used as monotherapy.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Padcev (enfortumab vedotin) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Padcev (enfortumab vedotin) may be authorized in quantities listed in the table below, until disease progression.

Treatment setting	Dose	Quantity
First-line in combination with Keytruda (pembrolizumab)	Up to 125 mg per dose	Up to two doses every 21 days
Subsequent line as monotherapy	Up to 125 mg per dose	Up to three doses every 28 days

C. Authorization **may** be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

IV. Padcev (enfortumab vedotin) is considered investigational when used for all other conditions.

Position Statement

Summary

- Padcev (enfortumab vedotin) is an intravenously administered antibody-drug conjugate that delivers cytotoxic chemotherapy to cells that express nectin-4 (e.g., bladder cancer cells).
- It is indicated as monotherapy for use in patients with advanced (unresectable locally advanced or metastatic) urothelial carcinoma (UC; bladder cancer) when disease progresses after therapy with platinum-based chemotherapy (unless ineligible for platinum-based therapy) and a PD-1/PD-L1 inhibitor, and in combination with Keytruda (pembrolizumab) as a front-line therapy for locally advanced or metastatic UC.
- The intent of this policy is to allow coverage of Padcev (enfortumab vedotin) for patients with advanced (locally advanced or metastatic) UC as a monotherapy for disease that has progressed on or after prior therapy in the advanced setting, or in combination with Keytruda (pembrolizumab) as a front-line therapy for patients who are not eligible for cisplatin-containing chemotherapy, up to the dose shown to be safe and effective in clinical trials.
- The evidence for Padcev (enfortumab vedotin) in combination with Keytruda (pembrolizumab) as a front-line therapy for locally advanced or metastatic UC is based on a randomized controlled trial (RCT) that demonstrated a clinically relevant improvement in overall survival (OS) relative to a standard of care platinum-based chemotherapy regimen. However, it is not known how Padcev (enfortumab vedotin) plus Keytruda (pembrolizumab) compares with front-line platinum-based chemotherapy followed by maintenance therapy with a PD-1 inhibitor, a combination which has also been shown to improve median OS relative to platinum-based chemotherapy alone. Additionally, the use of front-line Padcev (enfortumab vedotin) plus Keytruda (pembrolizumab) has not been compared with the sequential use of these two medications.
- The use of Padcev (enfortumab vedotin) as a monotherapy in the subsequent-line therapy for locally advanced or metastatic UC is based on a small, single-arm trial that measured tumor response rates (early-phase, low quality evidence). All of the patients in the trial had disease progression on prior therapy with platinum-based chemotherapy and a PD-1 or PD-L1 inhibitor.
- A confirmatory trial later showed that Padcev (enfortumab vedotin) improves median overall survival (OS) relative to single-agent chemotherapy (e.g., docetaxel or paclitaxel) in patients with locally advanced or metastatic bladder cancer who had disease progression during or after cytotoxic chemotherapy and immune checkpoint inhibitor therapy (PD-1 or PD-L1 inhibitors).

- Padcev (enfortumab vedotin) has a boxed warning describing the risk of potentially serious and fatal skin reactions. Similar to chemotherapy, it may cause nausea and vomiting, fatigue, neutropenia and infections. Additionally, high blood glucose (including diabetes mellitus and diabetic ketoacidosis), and peripheral neuropathy have been reported.
- The NCCN bladder cancer guideline lists Padcev (enfortumab vedotin) among potential therapies for locally advanced or metastatic bladder cancer in the treatment settings described above. In the front-line setting the strongest guideline recommendations are for chemotherapy followed by maintenance therapy with Bavencio (avelumab).
- Padcev (enfortumab vedotin) is given via IV infusion over 30 minutes at a dose of 1.25 mg/kg (maximum of 125 mg per dose). As monotherapy it is given every week for 3 consecutive weeks out of every 28-day cycle. When given in combination with Keytruda (pembrolizumab) it is given weekly for 2 consecutive weeks out of each 21-day cycle. It is administered until disease progression or unacceptable toxicity.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy

- The approval of Padcev (enfortumab vedotin) was based on a small, single-arm, non-blinded study in patients with locally advanced or metastatic urothelial carcinoma (bladder cancer) who had two prior lines of therapy for their disease. [1,2] The overall quality of this evidence is poor.
    * All patients had prior therapy with a platinum-based chemotherapy regimen and a checkpoint inhibitor (either a PD-1 or PD-L1 inhibitor). The chemotherapy was administered in the adjuvant or neoadjuvant setting if there was progression within 12 months, or in the locally advanced or metastatic disease settings.

    * Additional characteristics of patients enrolled in the trial included good performance status, no active CNS disease, no sensory or motor neuropathy, and no uncontrolled diabetes.
    * The trial evaluated tumor response (overall response rate) as the primary endpoint. Tumor response (stabilization of shrinking of tumor size on an x-ray) has not been shown to accurately predict improvement in survival, function, or quality of life in the advanced bladder cancer setting.
    * Approximately one in three patients enrolled in the trial stopped treatment for reasons other than meeting a study endpoint (an adverse event, or physician or patient decision).
- A confirmatory trial later showed that Padcev (enfortumab vedotin) improves median overall survival (OS) in this population. [3]
    * Patients with locally advanced or metastatic urothelial carcinoma who had disease progression on a platinum-based chemotherapy regimen and a check-point inhibitor (either a PD-1 or PD-L1 inhibitor) were randomized (N=608) to receive either Padcev (enfortumab vedotin) or single-agent chemotherapy (docetaxel, paclitaxel, or vinflunine).
    * The median age of patients in the trial was 68 years. Seventy-seven percent of the population were men. Seventy-eight percent had visceral disease.
    * The median OS, the primary endpoint, was 12.9 months and 9.0 months in the Padcev (enfortumab vedotin) and chemotherapy treatment arms, respectively. [HR for death, 0.70 (95% CI: 0.56, 0.89); p=0.001]
- Padcev (enfortumab vedotin) was also evaluated as a front-line therapy for locally advanced or metastatic UC in combination with Keytruda (pembrolizumab) [Study EV-302/ KEYNOTE-A39]. The evidence is based on a large (N=886), open-label RCT that compared this combination with a platinum-based chemotherapy regimen. [4]
    * Patients enrolled in the study had no prior therapy for advanced disease and were eligible to receive platinum-based chemotherapy. Prior neoadjuvant or adjuvant chemotherapy was allowed if there had been no disease recurrence within 12 months after its completion.
    * Padcev (enfortumab vedotin) was given in 21-day cycles until disease progression. Keytruda (pembrolizumab) was given in 21-day cycles until disease progression or for a maximum of 35 cycles (2 years).
    * Ninety-five percent of the population had metastatic disease. Approximately 27% had upper tract UC while the remaining 73% had lower tract UC.
    * The median OS was 31.5 months and 16.1 months in the Padcev (enfortumab vedotin) plus Keytruda (pembrolizumab) and chemotherapy treatment arms, respectively.

Guidelines [5]

- The NCCN bladder cancer guideline lists the following recommendations for locally advanced or metastatic UC (bladder cancer):
    * *Front-line:* Preferred, category 1 recommendations include cisplatin plus gemcitabine followed by Bavencio (avelumab) maintenance, and dose-dense methotrexate/vinblastine/doxorubicin/cisplatin followed by Bavencio (avelumab).

Padcev (enfortumab vedotin) plus Keytruda (pembrolizumab) is included as a category 2A recommendation, including in patients ineligible for cisplatin.

* *Second- and subsequent-line:* Keytruda (pembrolizumab) after initial therapy with a platinum-containing regimen when used as monotherapy [preferred, category 1]; and Padcev (enfortumab vedotin) monotherapy is listed among several category 2A recommendations.

Investigational Uses

- Padcev (enfortumab vedotin) is a nectin-4-directed antibody-drug conjugate (ADC). Nearly all bladder cancers overexpress this protein. There is interest in using this ADC in other types of cancer that overexpress nectin-4 (e.g., ovarian cancer, hepatocellular carcinoma); however, there is no evidence to support the use of enfortumab vedotin (Padcev) outside of the locally advanced or metastatic bladder cancer setting at this time.

Safety [6]

- Since its initial approval, Padcev (enfortumab vedotin) has picked up a boxed warning for serious skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN).
- Systemic adverse events (AEs) occurred with a high frequency in the Padcev (enfortumab vedotin) pivotal trial:
  * Grade 3 and 4 AEs occurred in 68% of patients.
  * Dose reductions were required in 34% of the patients.
  * The discontinuation rate due to AEs was 16%.
  * The most common serious AEs included urinary tract infections, cellulitis, febrile neutropenia, diarrhea, sepsis, acute kidney injury, dyspnea, and rash.
  * Peripheral neuropathy occurred in 56% of patients. Four percent of these cases were Grade 3 or 4 AEs.
  * Grade 3 or 4 hyperglycemia occurred in 8% of patients.
- There is a greater risk of AEs when Padcev (enfortumab vedotin) is used in combination with Keytruda (pembrolizumab) based on a significant numerical increase in overall AEs observed across studies; however, the difference is difficult to accurately quantify as there were no direct comparators in the combination study.

Dosing [6]

- The labeled dose of Padcev (enfortumab vedotin) is 1.25 mg/kg, up to a maximum of 125 mg per dose. It is given via intravenous infusion with the following frequency:
  * ***Monotherapy:*** On Days 1, 8, and 15 of every 28-day cycle until disease progression or unacceptable toxicity.
  * ***In combination with Keytruda (pembrolizumab):*** On Days 1, and 8 of every 21-day cycle until disease progression or unacceptable toxicity
- Doses are withheld, adjusted, or discontinued based on the severity of certain side effects (e.g., hyperglycemia, peripheral neuropathy, skin reactions). Refer to package labeling for specific recommendations.

Appendix 1: PD-1 and PD-L1 Inhibitors Indicated for Use in Bladder Cancer

PD-1 Inhibitors	PD-L1 Inhibitors
Opdivo (nivolumab)	Tecentriq (atezolizumab)
Keytruda (pembrolizumab)	Bavencio (avelumab)

Cross References
Adstiladrin, nadofaragene firadenovec, Medication Policy Manual, Policy No. dru743
Balversa, erdafitinib, Medication Policy Manual, Policy No. dru593
Bavencio, avelumab, Medication Policy Manual, Policy No. dru499
Jelmyto, mitomycin for pyelocaliceal solution (hydrogel), Medication Policy Manual, Policy No. dru637
Keytruda, pembrolizumab, Medication Policy Manual, Policy No. dru367
Opdivo, nivolumab, Medication Policy Manual, Policy No. dru390
Tecentriq (atezolizumab), Medication Policy Manual, Policy No. dru463

Codes	Number	Description
HCPCS	J9177	Injection, enfortumab vedotin-ejfv (Padcev), 0.25 mg

References

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6. Padcev® (enfortumab vedotin-ejfv) [package insert]. Seagen Inc.; Bothell, WA; December 2023.

Revision History

Revision Date	Revision Summary
6/20/2024	• Added 'in the locally advanced or metastatic disease setting' to UC, first-line criterion II.B.1.a to clarify intent. • Corrected the quantity limits under Quantity Limitations (III.B). (the approvable quantities for the two covered settings were reversed). No change to intent.
12/7/2023	No criteria changes with this annual review.
9/14/2023	Added coverage criteria for use in locally advanced or metastatic urothelial carcinoma when used in combination with Keytruda (pembrolizumab) as a front-line therapy for patients who are not eligible for cisplatin-containing chemotherapy.
12/9/2022	• Updated standard language in policy. • Changed coverage criteria to allow waiving the requirement for prior platinum-based chemotherapy if a patient is ineligible for this type of therapy.
1/20/2021	Updated continuation of therapy (COT) language. No changes to coverage criteria.
4/22/2020	New policy (effective 05/15/2020). Limits coverage to patients with unresectable locally advanced or metastatic urothelial carcinoma (bladder cancer) in patients whose disease progressed after front-line platinum-based chemotherapy and second-line checkpoint inhibitor therapy (PD-1/PD-L1 inhibitor therapy), the setting in which it was studied and has a labeled indication.

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Medication Policy Manual | **Policy No:** dru623

Topic: Enhertu, fam-trastuzumab deruxtecan-nxki | **Date of Origin:** May 15, 2020

Committee Approval Date: March 6, 2025 | **Next Review Date:** 2025

Effective Date: May 1, 2025

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Enhertu (fam-trastuzumab deruxtecan-nxki) is an intravenous (IV) medication used for certain types of cancer. It is an antibody-drug conjugate that delivers chemotherapy to cancer cells that express human epidermal growth factor receptor 2 (HER2).

Policy/Criteria

Most contracts require pre-authorization approval of Enhertu (fam-trastuzumab deruxtecan-nxki) prior to coverage.

I. Continuation of therapy (COT): Enhertu (fam-trastuzumab deruxtecan-nxki) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Enhertu (fam-trastuzumab deruxtecan-nxki) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that one of the following below (A, B, C, or D) is met:

A. A diagnosis of **locally advanced or metastatic gastric or gastroesophageal junction (GEJ) cancer** when criteria 1 through 3 below are met:

1. The tumor is human epidermal growth factor 2 (HER2)-positive**.**

AND

2. There has been disease progression on, or after, two or more prior lines of therapy in the advanced disease setting, which must have included all of the following (a through c):

a. Trastuzumab.

AND

b. A platinum (such as cisplatin, carboplatin, or oxaliplatin).

AND

c. A fluoropyrimidine [such as fluorouracil (5-FU) or capecitabine.

AND

3. The patient has not had prior treatment with Enhertu (fam-trastuzumab deruxtecan-nxki).

OR

B. A diagnosis of **unresectable or metastatic breast cancer** in one of the following two settings (1 or 2):

1. There is documentation that the tumor is **HER2-positive** and all of the following criteria are met (a and b):

a. There has been disease progression on a prior HER2-directed therapy in one of the following two settings (refer to *Appendix 1*):

i. In the metastatic setting,

OR

ii. In the neoadjuvant or adjuvant setting after disease recurrence during or within six months of completing therapy.

AND

b. The patient has not had prior treatment with Enhertu (fam-trastuzumab deruxtecan-nxki).

OR

2. There is documentation that the tumor is **HER2-low (IHC 1+ or IHC 2+/ISH-negative)** and all of the following criteria are met (a through d):

[IHC = immunohistochemistry; ISH = in situ hybridization]

a. There has been disease progression on prior cytotoxic chemotherapy for metastatic disease, or within six months of completing adjuvant chemotherapy (see *Appendix 2*).

AND

b. If the disease is hormone receptor-positive (HR+), there has been disease progression on at least one prior line of endocrine therapy (see *Appendix 3*).

AND

c. Enhertu (fam-trastuzumab deruxtecan-nxki) will be used as monotherapy.

AND

d. The patient has not had prior treatment with Enhertu (fam-trastuzumab deruxtecan-nxki).

OR

C. A diagnosis of **unresectable or metastatic non-small lung cancer (NSCLC)** when criteria 1 through 4 below are met:

1. There has been disease progression on at least one prior systemic therapy given in the metastatic disease setting.

AND

2. Documentation of an activating HER2 (ERBB2) mutation as defined at oncokb.org.

AND

3. Enhertu (fam-trastuzumab deruxtecan-nxki) will be used as monotherapy.

AND

4. No prior treatment with a HER2-directed antibody (e.g., trastuzumab) or antibody-drug conjugate [e.g., Enhertu (fam-trastuzumab deruxtecan-nxki) or Kadcyla (ado-trastuzumab emtansine)].

OR

D. A diagnosis of **unresectable locally advanced or metastatic biliary tract cancer (BTC)** [includes gallbladder carcinoma, intrahepatic cholangiocarcinoma, and extrahepatic cholangiocarcinoma] when criteria 1 through 4 below are met:

1. There has been progression or recurrence of disease on or after at least one prior cytotoxic chemotherapy regimen used in the advanced disease setting.

AND

2. The tumor is HER2-postive as defined by an immunohistochemical score of 3+ (IHC 3+).

AND

3. There has been no prior use of HER2-directed therapy (refer to *Appendix 1)*.

AND

4. Enhertu (fam-trastuzumab deruxtecan) will be used as monotherapy.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Enhertu (fam-trastuzumab deruxtecan-nxki) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Enhertu (fam-trastuzumab deruxtecan-nxki) may be authorized in the following quantities:

1. Breast cancer, NSCLC, BTC, and HER2-positive unresectable or metastatic solid tumors: Up to one infusion (5.4 mg/kg) every 21 days until disease progression.

2. Gastric or GEJ cancer: Up to one infusion (6.4 mg/kg) every 21 days until disease progression.

C. Authorization **may** be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

IV. Enhertu (fam-trastuzumab deruxtecan-nxki) is considered investigational when used for all other conditions, including but not limited to:

A. Non-small cell lung cancer (NSCLC) with a HER2 mutations not considered 'oncogenic or likely oncogenic' as defined at oncokb.org.

B. HER2-low breast cancer when used in the front-line setting.

C. HER2-positive (IHC 3+) solid tumors not specifically described in the coverage criteria (Section II.) above.

Position Statement

Summary

- Enhertu (fam-trastuzumab deruxtecan-nxki) is an intravenously administered antibody-drug conjugate that delivers cytotoxic chemotherapy to cells that express the human epidermal growth factor receptor 2 (HER2). It is indicated for use in:
  * Unresectable or metastatic **HER2-positive** breast cancer after the disease has progressed on at least two prior lines of HER2-directed therapy.
  * Unresectable or metastatic **HER2-low** breast cancer after progression on at least one prior line of chemotherapy
  * Locally advanced or metastatic **HER2-positive** gastric or GEJ cancer after the disease has progressed on a prior trastuzumab-containing regimen.
  * Unresectable or metastatic non-small cell lung cancer (NSCLC) in tumors that have **HER2 (ERBB2) mutations** when disease has progressed on or after at least one prior systemic therapy.
  * It also received an indication for patients with unresectable locally advanced or metastatic HER2-positive (IHC 3+) solid tumors after prior therapy when there are no remaining satisfactory treatment options.
- The intent of this policy is to cover Enhertu (fam-trastuzumab deruxtecan-nxki) in settings where it has been shown to be safe and effective, as detailed in the coverage criteria, with consideration for other available treatment options.
  * Where there is lack of proven additional benefit and/or lack of demonstrated health outcome (such as overall survival or improved quality of life) relative to alternative therapies, use of Enhertu (fam-trastuzumab deruxtecan-nxki) is not coverable ("not medically necessary" or "investigational").
  * It is important to note that the fact that a medication is FDA approved for a specific indication does not, in itself, make the treatment medically reasonable and necessary.

- Enhertu (fam-trastuzumab deruxtecan-nxki) also FDA approved for use in the following conditions; however, the health plan considers these uses to be "investigational" (not covered) as Enhertu (fam-trastuzumab deruxtecan-nxki) has not demonstrated to provide any health benefit, based on the currently available evidence:
    * Unresectable locally advanced or metastatic HER2-positive (IHC 3+) solid tumors after prior therapy when there are no remaining satisfactory treatment options *(as described in the Clinical Efficacy section below).*
- Many of the clinical indications for Enhertu (fam-trastuzumab deruxtecan-nxki) have been approved by the FDA and endorsed by clinical guidelines based on surrogate measures such as overall tumor response rate (ORR) and progression-free survival (PFS) which are not proven to accurately predict clinically important outcomes such as improved overall survival or improved quality of life.
- Like other HER2-based chemotherapy regimens, Enhertu (fam-trastuzumab deruxtecan-nxki) is associated with significant side effects including decreased blood counts (e.g., neutropenia, anemia, thrombocytopenia), gastrointestinal effects (nausea, vomiting, diarrhea), fatigue. It also has a boxed warning for interstitial lung disease (ILD) and pneumonitis, a serious side effect that occurs in one in ten to eleven patients who use this medication.
- NCCN guidelines list Enhertu (fam-trastuzumab deruxtecan-nxki) among potential treatment options in the settings in which it has been approved and studied.
- Enhertu (fam-trastuzumab deruxtecan-nxki) is given via IV infusion every 3 weeks until disease progression or unacceptable toxicity.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy

GASTRIC/GEJ CANCER

- The efficacy of Enhertu (fam-trastuzumab deruxtecan-nxki) in gastric/GEJ cancer was evaluated in a phase 2, randomized, open-label trial conducted in Asia. [1] All patients had HER2-positive locally advanced or metastatic gastric or GEJ cancer that had progressed after at least two prior trastuzumab-based regimens. An increase in overall survival was seen in patients treated with fam-trastuzumab deruxtecan-nxki.
    * Patients had HER2-positive locally advanced or metastatic gastric or GEJ adenocarcinoma who had progressed on and after at least two prior regimens including trastuzumab, a fluoropyrimidine- and a platinum-containing chemotherapy.
    * Patients received treatment with fam-trastuzumab deruxtecan-nxki or physician's choice of chemotherapy (irinotecan monotherapy or paclitaxel monotherapy).
    * Overall survival (OS) was 12.5 months with fam-trastuzumab deruxtecan-nxki compared to 8.4 months with chemotherapy.
- NCCN guidelines for gastric and GEJ cancer include Enhertu (fam-trastuzumab deruxtecan-nxki) in HER2-positive gastric or GEJ cancer as a preferred regimen in second-line or subsequent therapy (category 2A) in unresectable locally advanced or metastatic disease. Other preferred regimens in the second line setting include ramucirumab/paclitaxel, docetaxel, paclitaxel, irinotecan (all category 1), and fluorouracil/irinotecan (category 2A). [2]

BREAST CANCER

- The efficacy of Enhertu (fam-trastuzumab deruxtecan-nxki) in patients with unresectable or metastatic **HER2-positive** breast cancer is based on a small, single-arm, non-blinded study that measured tumor response rates (early-phase, low-quality evidence). All patients enrolled in the clinical study had prior therapy with trastuzumab and Kadcyla (ado-trastuzumab emtansine). [3,4] The overall quality of evidence is poor. Shrinking or stabilizing the size of a tumor (measured using an x-ray) has not been shown to accurately predict relevant clinical outcomes such as improvement in survival, function, or quality of life. Additional studies are needed to show that this new therapy improves patient health. Because there was no comparator in the study, it is not known if Enhertu (fam-trastuzumab deruxtecan-nxki) is better than other HER2-based chemotherapy regimens used in the HER2-positive metastatic breast cancer setting.
    * All of the patients in the trial had prior therapy with both a trastuzumab-containing regimen and Kadcyla (ado-trastuzumab emtansine), both anti-HER-2 therapies. In addition, 66% of subjects had prior Perjeta (pertuzumab) and 54% had another anti-HER2 therapy.
    * Patients were required to have good performance status, a left ventricular ejection fraction of at least 50%, and no history of noninfectious interstitial lung disease. Additionally, patients with untreated or symptomatic brain metastasis were not allowed to enroll in the trial.

    * The trial evaluated tumor response (overall response rate) as the primary endpoint. Tumor response (stabilization of shrinking of tumor size on an x-ray) has not been shown to accurately predict improvement in survival, function, or quality of life in the metastatic breast cancer setting. Additional trials are needed to establish clinical benefit.

- The efficacy of Enhertu (fam-trastuzumab deruxtecan-nxki) was also studied in a phase 3, open-label, randomized trial compared to Kadcyla (ado-trastuzumab emtansine) in patients with HER2-positive breast cancer previously treated with trastuzumab and a taxane. At the time of the analysis, progression-free survival (PFS) was not reached in the fam-trastuzumab deruxtecan-nxki group and was 6.8 months in the trastuzumab emtansine group. [5]
    * All of the patients in the trial had unresectable or metastatic breast cancer that had progressed during or after treatment with trastuzumab and a taxane in the context of advanced or metastatic disease or that had progressed within 6 months after neoadjuvant or adjuvant treatment involving trastuzumab or a taxane.
    * The primary endpoint of the trial was progression free survival (PFS). At the time of the study analysis, PFS was not reached for patients in the fam-trastuzumab deruxtecan-nxki group and was 6.8 months in the trastuzumab emtansine group. PFS has not been correlated with a clinically meaningful outcome such as overall survival (OS). OS data is not yet mature.
- The efficacy of Enhertu (fam-trastuzumab deruxtecan-nxki) as a second- or subsequent-line therapy for recurrent, unresectable and/or metastatic **HER2-low** (IHC 1+ or IHC 2+/ISH-negative) breast cancer was based on an open-label, randomized controlled trial [DESTINY-Breast04] where it demonstrated an overall survival (OS) advantage relative to physician's choice of chemotherapy. [6] Patients in the trial had disease progression on prior cytotoxic chemotherapy and, if the tumor was hormone receptor-positive (HR+), at least one prior line of endocrine therapy.
    * Eighty-nine percent of the patients enrolled in the trial had tumors that were hormone receptor-positive (HR+) while the other 11% had triple negative breast cancer (TNBC).
    * All patients were required to have had prior chemotherapy for metastatic disease or had recurrence within 6 months of completing adjuvant therapy (median of 3 prior therapies). Targeted therapies, including hormone-targeted therapy [anticancer endocrine therapy and CDK4/6 inhibitors] and immunotherapy, were not considered as prior systemic chemotherapy treatments. If the breast cancer was HR+, patients were also required to have had at least one prior line of hormone-targeted (endocrine) therapy (71% had a prior CDK4/6 inhibitor).
    * Of the 577 enrolled patients, 100% had prior treatments with cytotoxic chemotherapy, with 27% of patients with two prior lines of therapy in the metastatic setting, and 62% with three or more.

    * The median OS in the Enhertu (fam-trastuzumab deruxtecan-nxki) and chemotherapy treatment arms was 23.4 months and 16.8 months, respectively [HR 0.64 (95%CI: 0.49, 0.84); p = 0.001].
- The NCCN breast cancer guideline lists the following: [2]
    * Trastuzumab/Perjeta (pertuzumab) plus a taxane is listed as the preferred front-line therapy for recurrent or metastatic HER2-positive breast cancer. Enhertu (fam-trastuzumab deruxtecan-nxki) is listed as a second-line option, along with Kadcyla (ado-trastuzumab emtansine) in this setting.
    * The NCCN notes that Enhertu (trastuzumab deruxtecan-nxki) may be considered in the first-line setting as an option for patients with rapid progression within 6 months of neoadjuvant or adjuvant therapy.
    * The guidelines further note that regiments such as Enhertu (fam-trastuzumab deruxtecan-nxki) and Kadcyla (trastuzumab emtansine) may also be used as an option for third-line and beyond; optimal sequencing of HER2-directed therapies has not been determined.
    * Enhertu (trastuzumab deruxtecan-nxki) is also listed among preferred therapy options for recurrent, metastatic HER2-low breast cancer as a second- or subsequent-line treatment option.

NON-SMALL CELL LUNG CANCER (NSCLC)

- The efficacy of Enhertu (fam-trastuzumab deruxtecan-nxki) in relapsed or refractory advanced NSCLC with a HER2 (ERBB2) mutation was evaluated in cohorts from two open-label, single-arm studies that measured tumor response as a surrogate endpoint. [7,8] About half of the patients had a partial response with only 1% achieving a complete response. The evidence is of poor quality as there was no blinding or control, and tumor response has not been shown to accurately predict any clinically relevant benefit. Furthermore, it is not known which HER2 mutations may contribute to the NSCLC disease process.
    * Approximately half of the patients had a partial response while on therapy; however, only 1% achieved a complete response.
    * The evidence is of poor quality as there was no blinding or control, and tumor response has not been shown to accurately predict any clinically relevant benefit.
    * Furthermore, it is not known which HER2 mutations may contribute to the NSCLC disease process. The NCCN NSCLC guideline refers clinicians to an on-line resource to determine whether a particular HER2 mutation may be ‘oncogenic or likely oncogenic’.
- Confirmatory trials are needed to determine whether Enhertu (fam-trastuzumab deruxtecan-nxki) provides any clinical benefit in this setting.
- The NCCN NSCLC guideline lists Enhertu (fam-trastuzumab deruxtecan-nxki) as a preferred therapy for metastatic, HER2 (ERBB2)-mutant NSCLC after there has been disease progression on front-line therapies.

BILIARY TRACT CANCER (BTC)

- The efficacy of Enhertu (fam-trastuzumab deruxtecan-nxki) in relapsed or refractory advanced or metastatic, HER2-positive (IHC 3+) BTC is from two open-label, single-arm studies that evaluated tumor response as the endpoint. No patients included in the study had prior use of HER2-directed therapy. The evidence is of poor quality as there was no blinding or control, and tumor response has not been shown to accurately predict any clinically relevant benefit; however, coverage in this setting recognizes the current lack of treatment options available for this population.
    * One study [DESTINY-Pan Tumor02] enrolled 22 patients with advanced, HER2-positive (IHC 3+) BTC and reported an ORR of 44% [95% CI: 24, 48]. [7]
    * A second study [HERB; NCCH1805] enrolled 22 patients with advanced, HER2-positive (either IHC 3+, or IHC2+ and ISH+) BTC and reported an ORR of 36% [90%CI: 20, 56]. [9]
- Of the HER2-directed therapies available for use as subsequent-line treatment options for advanced BTC, each of which has similar low-quality evidence (all are single-arm, basket trial studies), Enhertu (fam-trastuzumab deruxtecan-nxki) is the most cost-effective treatment option.

Investigational Uses [10,11]

- Early-stage breast cancer: There is no published evidence for Enhertu (fam-trastuzumab deruxtecan-nxki) in early-stage breast cancer. To date, the only evidence is in the metastatic disease setting.
- Other HER2-expressing cancers where HER-2 (ERBB2) setting [other than listed in the coverage criteria]: There is interest in the use of Enhertu (fam-trastuzumab deruxtecan-nxki) for a variety of other HER2-expressing cancers where HER-2 (ERBB2) is considered an emerging biomarker, including colorectal cancer (CRC), bladder cancer, endometrial cancer, ovarian cancer as well as other solid tumors.
- HER2-positive (IHC 3+) tumor agnostic setting [other than listed in the coverage criteria]:
    * Use of Enhertu (fam-trastuzumab deruxtecan-nxki) in the HER2-positive (IHC 3+) tumor agnostic setting is considered investigational because its clinical efficacy is uncertain in this population. Available data is limited to small numbers of patients from an observational, single-arm study that did not represent all solid tumor types. Furthermore, it is uncertain whether HER2 overexpression drives tumor growth in all solid tumors [some tumors represented in the study had no response to Enhertu (fam-trastuzumab deruxtecan-nxki)]. Additional evidence is needed to determine whether there is clinical benefit in this heterogeneous population.
    * Enhertu (fam-trastuzumab deruxtecan-nxki) received a 'tumor agnostic' indication for patients with HER2-positive unresectable or metastatic solid tumors who have received prior systemic therapy and have no remaining satisfactory treatment options.

- The pivotal trial [DESTINY-PanTumor02] was a small (N=111), single-arm, observational study that evaluated objective response rate (ORR), a non-validated surrogate endpoint, in patients with a variety of locally advanced or metastatic tumors that were HER2-positive. [7,11]
- HER2-positive was defined as a 3+ score on immunohistochemistry (IHC) assay (IHC 3+).
- There is low reliability in the evidence of efficacy for Enhertu (fam-trastuzumab deruxtecan-nxki) in this broad, heterogeneous population for reasons that include, but are not limited to, the use of very small populations that may not be representative of the greater population with a given tumor type (most tumors were represented in fewer than 20 patients), the lack of representation of all types of HER2-positive solid tumors in the study, the lack of response observed in some tumor types (HER2 overexpression may not be a driver of tumor growth in all types of solid tumors), the lack of comparator in the study, and the use of a surrogate endpoint that does not reflect improvement in any clinically relevant outcome (e.g., improved overall survival or quality of life).
- For the reasons described above, the use of Enhertu (fam-trastuzumab deruxtecan-nxki) for HER2-postive (IHC3+) unresectable locally advanced or metastatic solid tumors is considered investigational. Additional evidence is needed to define its clinical benefit in this population.

Safety [4,7]

- Enhertu (fam-trastuzumab deruxtecan-nxki) carries a boxed warning for interstitial lung disease (ILD) and pneumonitis, and the potential for embryo-fetal harm. ILD may be fatal in a small proportion (2.6%) of patients.
- Serious treatment-emergent adverse effects (TEAEs) occurred in one in five patients receiving Enhertu (fam-trastuzumab deruxtecan-nxki) in clinical trials.
- About 1 in 10 patients discontinued Enhertu (fam-trastuzumab deruxtecan-nxki) due to AEs.
- The most commons serious AEs experienced with Enhertu (fam-trastuzumab deruxtecan-nxki) in clinical trials were decreased blood counts (neutropenia, anemia, thrombocytopenia), gastrointestinal effects (nausea, vomiting, diarrhea), fatigue, and asthenia.

Dosing [7]

- Enhertu (fam-trastuzumab deruxtecan-nxki) is given in a dose of 6.4 mg/kg in gastric/GEJ cancer and 5.4 mg/kg in all other coverable cancers. It is given via intravenous infusion every three weeks until disease progression or unacceptable toxicity.
- Dosing should be interrupted for interstitial lung disease (ILD) or pneumonitis, neutropenia, febrile neutropenia, and left ventricular dysfunction.

Appendix 1: HER2-Directed Agents (a.k.a. anti-HER2 therapies)

Infused (Medical benefit)	Oral (Prescription benefit)
trastuzumab (e.g., Herceptin; biosimilars Kanjinti, Ogivri, Trazimera)	Nerlynx (neratinib)
Enhertu (fam-trastuzumab deruxtecan)	Tukysa (tucatinib)
Perjeta (pertuzumab)	lapatinib (generic, Tykerb)
Kadcyla (ado-trastuzumab emtansine)	

NOTE: Pre-authorization is required for these products with the exception of the preferred version of trastuzumab (see dru620) and lapatinib (generic, Tykerb). Please see the Medication Policy page for a complete, up-to-date list.

Appendix 2: Cytotoxic Chemotherapy Agents Used in the Treatment of Advanced Breast Cancer [4] a,b	
"Preferred" Single Agents	***Chemotherapy Combinations***
Anthracyclines	AC: doxorubicin/cyclophosphamide
doxorubicin (generic, Adriamycin)	EC: epirubicin/cyclophosphamide
doxorubicin liposomal (generic, Doxil)	CMF: cyclophosphamide/methotrexate/fluorouracil
Taxanes	docetaxel/capecitabine
paclitaxel (generic, Taxol)	GT: gemcitabine/paclitaxel
Anti-metabolites	gemcitabine/carboplatin
capecitabine (generic, Xeloda)	paclitaxel/bevacizumab
gemcitabine (generic, Gemzar)	carboplatin + paclitaxel or albumin-bound paclitaxel
Other microtubule inhibitors	
vinorelbine (generic, Navelbine)	
eribulin (generic, Halaven)	
"Other" Single Agents	
cyclophosphamide (generic Cytoxan)	cisplatin
carboplatin	epirubicin
docetaxel (generic, Taxotere)	Ixempra (ixabepilone)
Abraxane (nab-paclitaxel)	Trodelvy (sacituzumab govitecan-hziy; for TNBC)

[a] Hormone-targeted therapies (endocrine therapy and CDK4/6s) are not considered "cytotoxic chemotherapy."

[b] Neoadjuvant/adjuvant regimens are not included, as finite regimens used for non-advanced disease. Examples: ddAC+T [doxorubicin/cyclophosphamide followed by paclitaxel], TC [docetaxel/ cyclophosphamide], or carboplatin/paclitaxel/pembrolizumab followed by AC/pembrolizumab.

Appendix 3: Endocrine Therapies Used in HR-Positive Advanced Breast Cancer		
Aromatase inhibitors (AIs)	**Selective estrogen receptor degraders (SERDs)**	**Selective estrogen receptor modifiers (SERMs)**
Arimidex (anastrozole)	Orserdu (elacestrant)	tamoxifen (Nolvadex, Soltamox)
Aromasin (exemestane)	Faslodex (fulvestrant)	
Femara (letrozole)		

Appendix 4: CDK4/6 Inhibitors Used in HR-Positive Advanced Breast Cancer
Verzenio (abemaciclib)
Ibrance (palbociclib)
Kisqali (ribociclib)

Cross References
BlueCross BlueShield Association Medical Policy, 5.01.20 - Pertuzumab for Treatment of Malignancies. [November 2022]
Cyramza, ramucirumab, Medication Policy Manual, Policy No. dru355
Kadcyla, ado-trastuzumab emtansine, Medication Policy Manual, Policy No. dru298
Nerlynx, neratinib, Medication Policy Manual, Policy No. dru520
pertuzumab-containing medications, Medication Policy Manual, Policy No. dru281
Products with Therapeutically Equivalent Biosimilars/Reference Products, Medication Policy Manual, Policy No. dru620
Trodelvy, sacituzumab govitecan-hziy, Medication Policy Manual, Policy No. dru645
Tukysa, tucatinib, Medication Policy Manual, Policy No. dru646

Codes	Number	Description
HCPCS	J9358	Injection, fam-trastuzumab deruxtecan-nxki (Enhertu), 1 mg

References

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Revision History

Revision Date	Revision Summary
3/6/2025	• Added coverage for use in advanced biliary tract cancer (BTC) after at least one prior systemic cytotoxic chemotherapy regimen when Enhertu (fam-trastuzumab deruxtecan) will be used as monotherapy and tumors are documented to be HER2-positive (IHC 3+). • Under the criteria for unresectable or metastatic breast cancer it was clarified that prior chemotherapy refers to 'cytotoxic' chemotherapy (criterion II.B.2.a).
9/19/2024	• Added supporting documentation to describe the rationale behind the investigational status for HER2-postive unresectable or metastatic solid tumors ('tumor agnostic' setting) [new indication]. Coverage will only be provided in settings specifically described in Section II. of the policy. • Added 'HER2-positive unresectable or metastatic solid tumors' under the 'Dosing, Quantity Limitations, and Authorization Period' section of the policy.
6/20/2024	Added 'in the advanced disease setting' to II.A.2 to clarify the intent of this criterion. No change to intent of coverage criteria with this annual review.
6/15/2023	No criteria changes with this annual update.
12/9/2022	• Added coverage criteria for patients with advanced HER2-low breast cancer in the second- or subsequent-line treatment setting (new indication). • Added coverage criteria for patients with advanced non-small cell lung cancer (NSCLC) with an activating HER2 (ERBB2) mutation as defined at oncokb.org. Use in HER2 mutations not considered 'oncogenic or likely oncogenic' as defined at oncokb.org will be considered investigational. • Updated formatting of other coverage criteria (no change to intent).
6/17/2022	Added coverage criteria for patients with unresectable or metastatic HER2-positive breast cancer after one prior anti-HER2-based regimen in the metastatic or neoadjuvant or adjuvant setting, a newly approved FDA indication.
7/16/2021	Added coverage criteria for patients with HER2-positive locally advanced or metastatic gastric or gastroesophageal junction cancer whose disease has progressed after a prior trastuzumab-based regimen, a newly approved FDA indication.
6/15/2020	Removed references to brand Herceptin (where applicable) from policy to account for upcoming changes in biosimilars policy (dru620).
4/22/2020	New policy (effective 5/15/2020). Limits coverage to patients with HER2-positive unresectable or metastatic breast cancer in patients whose disease progressed after at least two prior HER2-directed therapies, the setting in which it was studied and has a labeled indication.

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Medication Policy Manual | **Policy No:** dru625

Topic: Scenesse, afamelanotide | **Date of Origin:** May 15, 2020

Committee Approval Date: September 19, 2024 | **Next Review Date:** 2025

Effective Date: December 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Scenesse (afamelanotide) is a medication used to treat a rare genetic condition, erythropoietic protoporphyria (EPP), and the associated skin reaction. It is administered as a subcutaneous implant.

Policy/Criteria

Most contracts require pre-authorization approval of Scenesse (afamelanotide) prior to coverage.

I. Continuation of therapy (COT): Scenesse (afamelanotide) may be considered medically necessary for COT when full policy criteria below are met, including quantity limit.

Please note: *Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Scenesse (afamelanotide) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A, B, and C below are met.

A. A diagnosis of **erythropoietic protoporphyria** (EPP), in consultation with a specialist in hematology or dermatology.

AND

B. Documentation that one of the following (criterion 1 or 2) below are met:

1. Biochemical confirmation of both a and b below:

a. Elevated total erythrocyte protoporphyrin (≥ 80 mcg/dL).

AND

b. Increased proportion of erythrocyte metal-free protoporphyrin versus zinc protoporphyrin (≥ 85% of total erythrocyte protoporphyrin is metal-free).

OR

2. Molecular genetic testing consistent with a diagnosis of EPP (such as biallelic mutation on the ferrochelatase [FECH] gene).

AND

C. Documented phototoxic reactions from EPP have resulted in a significant complication including 1 or 2:

1. Skin maceration with secondary infection requiring anti-infective treatment (antibiotics or antifungals).

OR

2. Documentation of significant impact on quality of life or inability to perform critical activities of daily living (such as going outside to do errands or commuting to work/school) without experiencing significant pain due to phototoxic reactions from EPP.

PLEASE NOTE: Medical treatment of phototoxicity due to EPP is considered not medically necessary in the absence of significant medical complications associated with the condition. Skin irritation or erythema (skin redness) without pain/infection are not considered to be "significant medical complications."

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Scenesse (afamelanotide) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Scenesse (afamelanotide) will be authorized in quantities up to 4 implants per 48-weeks (based on usual dosing of 1 implant every 8 weeks during seasons of increased sunlight).

C. Authorization **may** be reviewed at least every 12 months to confirm that the medication is effective as documented by provider attestation or clinical documentation (e.g., decreased pain/severity and number of phototoxic reactions, increased duration of sun exposure, increased quality of life/ability to perform ADLs).

D. Additional treatments may be authorized on a case-by-case basis if documentation supports the need for more frequent dosing are provided (e.g., residence in a locale with year-round significant sun-exposure).

IV. Scenesse (afamelanotide) is considered not medically necessary when used for skin redness, vitiligo, or other cosmetic indications.

V. Scenesse (afamelanotide) is considered investigational when used for all other conditions, including but not limited to:

A. Solar urticaria.

Position Statement

Summary

- The intent of the policy is to limit coverage of Scenesse (afamelanotide) in erythropoietic protoporphyria (EPP) when symptoms are severe and significantly impact critical activities of daily living.
- Scenesse (afamelanotide) is a melanocortin-1 receptor agonist indicated for increasing pain-free light exposure in adults with a history of phototoxic reactions from EPP.
- The efficacy of Scenesse (afamelanotide) was established in two placebo-controlled randomized trials. Scenesse (afamelanotide) incrementally increased the amount of pain-free time patients were exposed to direct sunlight compared to placebo. However, the clinical relevance of the small change in pain-free time is unknown.
- Use of Scenesse (afamelanotide) for cosmetic purposes, primarily to improve or change appearance such as redness, is considered not medically necessary.
- There is insufficient evidence to support the use of Scenesse (afamelanotide) in any other condition.
- Scenesse (afamelanotide) may be covered for up to four 16 mg doses (subcutaneous implants) in a 48-week period to account for coverage during months when sunlight is the most prominent and intense (spring-fall). Although afamelanotide may be given every 2 months per label, symptoms of EPP manifest primarily due to sunlight exposure. Therefore, use of medication should be limited to before expected, and during increased, sunlight exposure (typically from spring to early autumn) in areas where the hours and intensity of sun exposure are significantly impacted by seasonality.

Background [1 2]

- Total erythrocyte protoporphyrin that is fractionated into non-complexed (metal-free) and zinc-complexed protoporphyrin is critical for an EPP diagnosis. The diagnosis of EPP is established by an abnormally high level of total erythrocyte protoporphyrin with a higher proportion of metal-free protoporphyrin versus zinc protoporphyrin. See appendix A for reference values. An 85% or higher proportion of metal-free is indicative of EPP.
- EPP is most commonly caused by autosomal recessive mutations in the gene encoding ferrochelatase (FECH). Genetic testing may confirm the diagnosis of EPP in the presence of two FECH gene mutations in trans. It is common to identify a FECH mutation on one allele, but clinical expression requires a hypomorphic FECH allele in trans with a more severe mutation. IVS3-48T->C (also referred to as c. 315-48T>C) is one hypomorphic variant of the FECH gene. C.1231T>G is a common severe FECH mutation. The presence of both c.1231T>G with c.315-48T>C or two copies of c.1231T>G are confirmatory for EPP. Although important, not all sequence variants have been validated as pathogenic, and a small number of pathogenic mutations are not detected by gene sequencing; therefore, the biochemical profile of porphyrin precursors remains the standard for diagnosis.

Clinical Efficacy

- Scenesse (afamelanotide) has been shown to increase pain-free light exposure in patients with erythropoietic protoporphyria (EPP) relative to placebo in two low-quality, phase 3, randomized-control trials. [3]
    * The placebo-controlled trials included adults with biochemically confirmed EPP who did not have any clinically significant organ dysfunction (including hepatic), skin cancer, or premalignant lesions.
    * The primary outcome of interest was duration of time in direct sunlight where patients reported they did not have pain.
    * In both studies, pain-free duration was marginally longer for patients on Scenesse (afamelanotide) versus placebo. In one study, there was a 24-hour difference between arms spread over a six-month period. In another study, the between arm difference was five hours within a nine-month span.[4]
- The mainstay of care for phototoxicity related to EPP is sun avoidance and use of protective clothing/physical barriers. Tanning creams which increase skin pigmentation or sunscreens which contain physical reflecting agents may be beneficial to some patients. [5]
- Narrow-band ultraviolet-B (UVB) phototherapy or beta-carotene may provide benefit, but efficacy data is limited to several small studies and case series.
- Patients should maintain sun and light protection measures during treatment with Scenesse (afamelanotide).
- The National Institute for Health and Care Excellence (NICE) notes that the marketing authorization in the United Kingdom recommends administering afamelanotide every 2 months before expected and during increased sunlight exposure for a maximum of 4 implants per year and that some people may not require four doses per year.[6]

Not Medically Necessary Uses

- Use of Scenesse (afamelanotide) for skin redness, vitiligo, or other cosmetic conditions is considered not medically necessary.

Investigational Uses

- Although Scenesse (afamelanotide) is being investigated in different skin disorders (such as solar urticaria), the quality of evidence from these studies are poor because they lack controls, are not randomized or blinded, and only involve small numbers of subjects.[7]

Safety [4]

- Scenesse (afamelanotide) was generally well-tolerated in clinical trials. Adverse reactions greater than 5% included implant site reactions, nausea, oropharyngeal pain, cough, and fatigue.
- Scenesse (afamelanotide) may induce darkening of pre-existing nevi and ephelides due to its pharmacological effect. A regular full body skin examination (twice yearly) is recommended.

Appendix A: Reference laboratory values indicative of EPP [8]		
Total erythrocyte protoporphyria	**Free protoporphyria**	**Zinc protoporphyria**
> 80 mcg/dL	<85% of total erythrocyte protoporphyria	<15% of total erythrocyte protoporphyria

Codes	Number	Description
HCPCS	J7352	Afamelanotide implant (Scenesse), 1 mg
ICD-10	E80.0	Hereditary erythropoietic porphyria

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Revision History

Revision Date	Revision Summary
9/19/2024	No changes to intent of coverage criteria with this annual update. Wording for criteria IIA updated to be consistent with other polices.
6/15/2023	No changes in coverage criteria with this annual update.
6/17/2022	No changes in coverage criteria with this annual update. Supporting statement updated with rationale for quantity limits. Updated quantity limits.
7/16/2021	Coverage criteria modified to include molecular genetic testing as an option for confirmation of disease.
4/22/2020	New policy (effective 5/15/2020). Coverage limited to confirmed diagnosis of erythropoietic protoporphyria with disease that significantly impacts activities of daily living.

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Medication Policy Manual | **Policy No:** dru628

Topic: Medications for Sickle Cell Disease | **Date of Origin:** May 15, 2020

- Adakveo, crizanlizumab-tmca
- Endari, L-glutamine
- Oxbryta, voxelotor

Committee Approval Date: June 20, 2024 | **Next Review Date:** 2025

Effective Date: September 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

This policy is for oral and injectable medications used in the treatment of sickle cell disease.

Policy/Criteria

Most contracts require pre-authorization approval of medications for sickle cell disease prior to coverage.

I. Continuation of therapy (COT): Medications for sickle cell disease may be considered medically necessary for COT when criterion A, B, or C **AND** D below is met.

A. For diagnoses NOT listed in the coverage criteria below, full policy criteria must be met for coverage.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

AND

D. ***[For Adakveo (crizanlizumab-tmca)]*** Site of care administration requirements are met [refer to Medication Policy Manual, *Site of Care Review*, dru408].

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. **For Endari (L-glutamine) new starts (treatment-naïve)**: The use of Endari (L-glutamine) is considered not medically necessary for the treatment of patients with **sickle cell disease** (SCD).

III. **For Oxbryta (voxelotor) new starts (treatment-naïve)**: The use of Oxbryta (voxelotor) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A through F below are met.

A. A diagnosis of **sickle cell disease** (SCD), established by or in consultation with a hematologist.

AND

B. The diagnosis of SCD has been confirmed by genetic testing (see *Appendix 1*).

AND

C. There has been at least one vaso-occlusive crisis (VOC) over the past 12 months.

AND

D. The patient's hemoglobin is ≤ 10.5 g/dL despite treatment with transfusion(s).

AND

E. Hydroxyurea has been ineffective after use for at least 6 months unless the use is not tolerated or is contraindicated. If unable to tolerate hydroxyurea, dose lowering attempts must be made to achieve the maximally tolerated therapeutic doses.

AND

F. For tablets for oral suspension: Documentation that the member weighs less than 40 kg or is unable to swallow tablets.

IV. **For Adakveo (crizanlizumab-tmca) new starts (treatment naïve):** The use of Adakveo (crizanlizumab-tmca) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A through E below are met.

A. A diagnosis of **sickle cell disease** (SCD), established by or in consultation with a hematologist.

AND

B. The diagnosis of SCD has been confirmed by genetic testing (see *Appendix 1*).

AND

C. There have been at least two vaso-occlusive crises (VOCs) over the past 12 months.

AND

D. Hydroxyurea has been ineffective after use for at least 6 months unless the use is not tolerated or is contraindicated. If unable to tolerate hydroxyurea, dose lowering attempts must be made to achieve the maximally tolerated therapeutic doses.

AND

E. Site of care administration requirements are met [refer to Medication Policy Manual, *Site of Care Review*, dru408].

V. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Adakveo (crizanlizumab-tmca) coverable only under the medical benefit (as a provider-administered medication).

B. Regence Pharmacy Services considers Endari (L-glutamine) and Oxbryta (voxelotor) coverable only under the pharmacy benefit (as self-administered medications).

C. When pre-authorization is approved, medications for sickle cell disease will be authorized in quantities and authorization periods as listed in Table 1.

VI. The use of Adakveo (crizanlizumab-tmca), Endari (L-glutamine), and Oxbryta (voxelotor) in combination with each other is considered investigational.

VII. Adakveo (crizanlizumab-tmca), Endari (L-glutamine), and Oxbryta (voxelotor) are considered investigational when used for all other conditions.

Table 1.

Quantity Limit/Authorization	Initial	Re-authorization
Adakveo (crizanlizumab-tmca): Up to 5mg/kg at week 0, week 2, and then every 4 weeks thereafter.	24 weeks	Continued authorization or re-authorization (after the initial 24-week period) **shall** be reviewed at least annually to confirm that current medical necessity criteria are met, the dose is within the dose limits, and that the medication is providing clinical benefit and that there is an improvement in disease activity, such as a decrease in VOC rate, compared to baseline.
Endari (L-glutamine): Up to three packets twice daily, not to exceed 30 grams per day.	24 weeks	Continued authorization or re-authorization (after the initial 24-week period) **shall** be reviewed at least annually to confirm that current medical necessity criteria are met, the dose is within the dose limits, and that the medication is providing clinical benefit and that there is an improvement in disease activity, such as a decrease in VOC rate, compared to baseline.
Oxbryta (voxelotor): Tablets: Up to three tablets per day, not to exceed 1500mg per day. Higher doses may be covered when there is concomitant use of a moderate or strong CYP3A4 inducer (up to 4 or 5 tablets per day, respectively). Tablets for oral suspension: • ≥40 kg: Up to 5 tablets per day. o With moderate or strong CYP3A4 inducer: up to 7 or 8 tablets per day, respectively. • 20 kg to less than 40 kg: Up to 3 tablets per day. o With moderate or strong CYP3A4 inducer: Up to 4 or 5 tablets per day, respectively. • 10 kg to less than 20 kg: Up to 2 tablets per day. o With moderate or strong CYP3A4 inducer: up to 3 tablets per day.	24 weeks	Continued authorization or re-authorization (after the initial 24-week period) **shall** be reviewed at least annually to confirm the dose is within the dose limits, the medication is providing clinical benefit, and there is an improvement in disease activity compared to baseline, such as improvement in hemoglobin level or anemia signs, symptoms, or complications.

Position Statement

Summary

- The medications covered by this policy (Adakveo, Endari, and Oxbryta) are used for the treatment of patients with sickle cell disease (SCD). All are used prophylactically to reduce disease burden.
- Sickle cell disease is a recessive hemolytic anemia, cause by a mutation in the ß-globin gene. It is characterized by the formation of sickle hemoglobin (HbS), which is less soluble and less elastic, than fetal hemoglobin (HbF) or normal adult hemoglobin (HbA). [1 2]
- Patients with SCD experience chronic anemia and severe, debilitating pain events, known as vaso-occlusive crises (VOCs). These VOCs are the most frequent cause of morbidity and mortality in SCD. [1 2]
- Chronic complications of SCD include pain, anemia, pulmonary hypertension, renal impairment, cardiac dysfunction, hepatotoxicity, neurologic issues, splenic dysfunction, and retinopathy.
- Hydroxyurea has established effectiveness and is recommended by treatment guidelines to decrease VOCs in patients with SCD. It is available generically and is a less costly alternative. [1]

<u>Crizanlizumab</u>

- Adakveo (crizanlizumab-tmca) is a monoclonal antibody that binds to P-selectin, and blocks interactions between endothelial cells, platelets, red blood cells, and leukocytes. P-selectin plays a role in the formation of the multicellular aggregates, that lead to vaso-occlusive crises (VOCs). [3]
- In a randomized, double-blind, placebo-controlled trial, patients with sickle cell disease (SCD) treated with Adakveo (crizanlizumab-tmca) had less VOCs compared to patients treated with placebo during 52 weeks of treatment. [4]
- However, a recent confirmatory randomized, double-blind, placebo-controlled trial has shown inconsistent results reporting no statistical differences between Adakveo (crizanlizumab-tmca) and placebo in the rate of annualized VOC's, leading to a questionable clinical benefit. [5]
- The intent of this policy is to allow for coverage of Adakveo (crizanlizumab-tmca) for patients with SCD when hydroxyurea is ineffective or not a treatment option, in individuals that continue to experience at least 2 VOCs per year.

<u>Voxelotor</u>

- Oxbryta (voxelotor) is a hemoglobin S (HbS) polymerization inhibitor. HbS polymerization during periods of deoxygenation, leads to sickling of red blood cells, a hallmark of sickle cell disease (SCD). [6]
- In a randomized, double-blind, placebo-controlled trial, patients with SCD treated with Oxbryta (voxelotor) had a greater improvement in hemolysis markers (such as hemoglobin, indirect bilirubin, and percent reticulocytes) compared to patients treated with placebo during 24 weeks of treatment. [7]

- The intent of this policy is to allow for coverage of Oxbryta (voxelotor) for patients with SCD that continue to experience anemia signs, symptoms, or complications despite treatment with alternatives. While Oxbryta (voxelotor) has been shown to improve hemoglobin, it has not been shown to decrease vaso-occlusive crises (VOCs). It was approved through the accelerated approval process, based on an improvement in hemoglobin level.

L-glutamine

- Endari (L-glutamine) is an amino acid indicated to reduce the acute complications of sickle cell disease (SCD) in adult and pediatric patients 5 years of age and older. L-glutamine may improve the nicotinamide adenine dinucleotide (NAD) redox potential in sickle red blood cells through increasing the availability of reduced glutathione. [8]
- In a randomized, double-blind, placebo-controlled trial, patients with SCD treated with Endari (L-glutamine) had less vaso-occlusive crises (VOCs) compared to patients treated with placebo during 48 weeks of treatment. L-glutamine has not been compared to other treatment alternatives. [9]
- The use of Endari (L-glutamine) for SCD is considered not medically necessary, given the lack of proven clinical benefit and significant trial limitations. Of note, other L-glutamine products are also available as over-the-counter supplements.

Clinical Efficacy

Crizanlizumab

- Safety and efficacy data for crizanlizumab was evaluated in a phase 2, multicenter, randomized, double-blind, placebo-controlled trial, the SUSTAIN trial. [4]
- The primary endpoint in SUSTAIN was annualized rate of vaso-occlusive crises (VOCs), also referred to as a sickle cell-related pain crises (SCPC), in adults with SCD. Time to first VOC event was considered a key secondary endpoint.
    * Subjects with 2 to 10 VOCs in the previous year were included in the trial.
    * VOC was defined as an acute episode of pain with no other medically determined cause than a vaso-occlusive event that requires a medical facility visit and treatment with oral or parenteral narcotics, or parenteral non-steroidal anti-inflammatory drugs. In addition, acute chest syndrome, hepatic/splenic sequestration, priapism, and death were considered to be a VOC.
- Results of the SUTAIN trial demonstrated that crizanlizumab reduces the number of VOCs in adult patients with SCD, compared to placebo.
    * The median annualized rate of VOCs was 1.63 and 2.98 in the crizanlizumab and placebo groups, respectively.
    * The median time to first VOC was 4.07 and 1.38 months in the crizanlizumab and placebo groups, respectively.
- There were no significant changes in quality of life (QOL) assessments, or in the markers for hemolysis (hemoglobin, reticulocytes, indirect bilirubin), between the crizanlizumab and placebo treated arms, during the trial.

- A recent report out in January 2023 from an unpublished, confirmatory phase 3 multicenter, randomized, double-blind, placebo-controlled trial, the STAND trial (N=254), has reported no statistical difference between Adakveo (crizanlizumab 5 mg/kg or 7.5 mg/kg) and that of placebo in reducing annualized rates of VOC's. [5]
- These results are inconsistent with what was reported from the above phase 2 SUSTAIN trial, thus making the true clinical benefit of Adakveo questionable, compared to placebo.

Voxelotor

- Voxelotor was granted priority review by the FDA, and was approved based on one phase 3, multi-center, double-blind, placebo controlled randomized controlled trial, the HOPE trial, which demonstrated an improvement in hemoglobin response at 24 weeks compared to placebo. [7]
    * Hemoglobin response was defined as the portion of subjects with increase in hemoglobin > 1g/dL from baseline at week 24.
- Results of the HOPE trial demonstrated that voxelotor improved markers of hemolysis, including hemoglobin, indirect bilirubin, and reticulocyte counts.
    * A total of 51% (46/90) and 7% (6/92) had a hemoglobin response at week 24, in the voxelotor 1500mg and placebo treated arms, respectively.
    * The change in indirect bilirubin was -29.1% and -3.2%, in the voxelotor 1500mg and placebo treated arms, respectively.
    * The change in percentage of reticulocytes was -19.9% and -1.3%, in the voxelotor 1500mg and placebo treated arms, respectively.
    * The threshold by which a reduction in hemolysis labs, is indicative of clinical benefit, is unknown.
    * A confirmatory trial is required by the FDA, which will assess if voxelotor can reduce cerebral blood flow velocity, and lead to a reduction in stoke risk.
- Longer-term follow-up in the HOPE trial demonstrated improvement in the markers of hemolysis through week 72. [10]
- Vaso-occlusive crisis (VOC) rate, a secondary endpoint, was not significantly different between the voxelotor and placebo treated arms. In addition, the clinical trial noted numerically more transfusions in the voxelotor group than in the placebo treated group, although this was not a pre-specified endpoint.
- QOL assessments were included as exploratory endpoints, however, no differences were observed between the voxelotor and placebo groups.

L-glutamine

- The efficacy of Endari (L-glutamine) was evaluated in one randomized, double-blind, placebo-controlled trial in patients ≥5 years of age with sickle cell anemia or beta thalassemia who had two or more painful crises within the previous twelve months. [9]
    * Patients previously stabilized on hydroxyurea could continue treatment throughout the study.

    * Patients treated with L-glutamine experienced less sickle cell crises (SCC) compared to patients treated with placebo (three vs. four, respectively) throughout the 48 weeks of the trial.
- High discontinuation rates and problems with the conduct and analysis in the L-glutamine trial reduce the certainty of the clinical benefit.
- There are no studies that compare L-glutamine to other treatment alternatives.

Safety

- The most common adverse events (incidence of 10% or more) reported during trials with Adakveo (crizanlizumab-tmca) were headache, back pain, nausea, arthralgia, UTI, pain in extremity, URI , pyrexia, diarrhea, and musculoskeletal pain. [3]
- The most common adverse events (incidence of 10% or more) reported during trials with Oxbryta (voxelotor) were headache, diarrhea, nausea, arthralgia, URI, abdominal pain, fatigue, rash, pyrexia, pain in extremity, back pain, and vomiting. [6]
- The most common adverse events (incidence of 10% or more) reported with Endari (L-glutamine) were constipation, nausea, headache, abdominal pain, cough, pain in extremity, back pain, and chest pain. [8]

Appendix 1: Sickle Cell Disease Types [1 2]
homozygous hemoglobin SS (HbSS)
heterozygous hemoglobin S β^0-thalassemia (HbSβ^0 -thalassemia)
hemoglobin Sβ^+ -thalassemia (HbSβ^+ -thalassemia)
hemoglobin SC disease (HbSC)

Cross References
Gene therapies for sickle cell disease, Medication Policy Manual, Policy No. dru766
Site of Care Review, Medication Policy Manual, Policy No. dru408

Codes	**Number**	**Description**
HCPCS	J0791	Injection, crizanlizumab-tmca (Adakveo), 5 mg

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Revision History

Revision Date	Revision Summary
6/20/2024	Updated cross references, no changes to criteria with this annual review.
6/15/2023	Removed Adakveo (crizanlizumab-tmca) step for Oxbryta (voxelotor).
6/17/2022	• Added Oxbryta (voxelotor) coverage criteria. • Updated Adakveo (crizanlizumab-tmca) coverage criteria to require at least two vaso-occlusive crises (rather than more than two) to coincide with trial inclusion criteria.
7/16/2021	• Addition of *Appendix 1*: Sickle cell disease types. • No criteria changes with this annual update. • COT updated to standard format, no change to intent.
7/22/2020	No changes to criteria with this annual update.
4/22/2020	New policy, effective 5/15/2020.

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Medication Policy Manual

Policy No: dru630

Topic: Givlaari, givosiran

Date of Origin: May 15, 2020

Committee Approval: June 20, 2024

Next Review Date: 2025

Effective Date: October 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Givlaari (givosiran) is a medication used to treat a rare condition, acute hepatic porphyria (AHP), and reduce disease flare ups. It is an injectable medication (administered subcutaneously) by a healthcare provider.

Policy/Criteria

Most contracts require pre-authorization approval of Givlaari (givosiran) prior to coverage.

I. Continuation of therapy (COT): Givlaari (givosiran) may be considered medically necessary for COT when full policy criteria below are met, including quantity limit.

Please note: *Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Givlaari (givosiran) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A through F below are met.

A. Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, Site of Care Review, dru408].

AND

B. A diagnosis of **acute hepatic porphyria** (AHP) [including acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), variegate porphyria (VP), and aminolevulinic acid dehydratase porphyria (ADP)].

AND

C. The diagnosis of AHP is established by or in consultation with a hepatologist, hematologist, gastroenterologist, or neurologist.

AND

D. The diagnosis of AHP has been confirmed by genetic testing, with documentation of a mutation in one of the following genes:

1. Hydroxymethylbilane synthase (diagnostic for AIP).
2. Coproporphyrinogen oxidase (diagnostic for HCP).
3. Protoporphyrinogen oxidase (diagnostic for VP).
4. Aminolevulinic acid dehydratase (diagnostic for ADP).

AND

E. Documentation of recurrent AHP, defined as greater than four attacks per year.

PLEASE NOTE: An attack is defined as a disease exacerbation requiring hospitalization, urgent healthcare visit, or administration of IV hemin (Panhematin) at home.

AND

F. Documentation of an evaluation to assess for underlying conditions or triggers for AHP (see *Appendices 1 and 2*). If identified, a documented plan is in place to address.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Givlaari (givosiran) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Givlaari (givosiran) may be authorized up to 2.5mg/kg per month.

C. Authorization shall be reviewed as follows:

1. **Initial Authorization:** Shall be for 6 months.

2. **Continued Authorization:** After initial reauthorization, authorization **shall** be reviewed at least annually (every 12 months). Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, including a decrease in AHP attack rates (defined above) compared to baseline and reduction in the need for additional treatment, such as hospitalization, urgent healthcare visits, or need for IV hematin.

IV. Givlaari (givosiran) is considered investigational when used for all other conditions.

Position Statement

Summary [1 2]

- The intent of the policy is to allow for coverage of Givlaari (givosiran) for recurrent acute hepatic porphyria (AHP), the condition for which it has been studied, when managed by a specialist (as outlined in the coverage criteria), and to limit coverage to doses studied and shown to be safe and effective in clinical trials.
- AHP is a family of rare metabolic diseases involving the heme biosynthesis pathway. AHP consists of four distinct subtypes [acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), variegate porphyria (VP), and aminolevulinic acid dehydratase porphyria (ADP)].
- Each AHP subtype involves a distinct enzymatic mutation within the pathway.
  * In AIP, HCP, and VP, these mutations reduce enzymatic activity to about 50% that of a normal patient.
  * With ADP, enzymatic activity is reduced to less than 5%.
- The first enzyme in the heme pathway, aminolevulinic acid synthase 1 (ALAS1), can be induced by numerous external triggers. An induction in ALAS1 results in the increased production of aminolevulinic acid (ALA) and porphobilinogen (PBG), two neurotoxic heme intermediates.
- The accumulation of ALA and PBG results in painful neurovisceral attacks, which consist of severe abdominal pain, peripheral neuropathy, tachycardia, hypertension, sweating, insomnia, bladder dysfunction and potential CNS involvement.

- AHP episodes are often triggered by an exacerbating factor, such as alcohol, smoking, certain medications (barbiturates, phenytoin, rifampin, etc.), lack of nutrition, hormonal fluctuations, and stress. Education and avoidance of precipitating factors is key to prevention of AHP attacks.
- A mutation in the heme biosynthesis pathway diagnostic of AHP, is relatively common, however the majority of patients are asymptomatic. Symptomatic AHP occurs in about ten per 1,000,000 patients, and disproportionately impacts women in their second through fourth decades of life.
- The majority of symptomatic AHP patients present with sporadic attacks. Only 3 to 8% of symptomatic patients have recurrent attacks, defined as greater than four attacks per year. It is this small subpopulation with frequent recurrent attacks which may benefit from Givlaari (givosiran).
- During clinical trials, Givlaari (givosiran) use resulted in a clinically relevant decrease in the annualized attack rate and use of emergency hemin in patients with AHP as compared to placebo.
- Givlaari (givosiran) was only studied in symptomatic patients with greater than two attacks within the last six months. The safety and efficacy in asymptomatic or less active disease is unknown.
- Additional controlled trials are needed to assess the long-term safety and efficacy of Givlaari (givosiran), including improvement in quality of life (QOL), overall survival, impact on long-term complications, or benefit over existing treatment options.
- Givlaari (givosiran) may be covered in doses up to 2.5mg/kg every month for AHP, the dose at which it has been shown to be safe and effective.

Clinical Efficacy [3]

The safety and efficacy of givosiran in recurrent AHP was established based on one phase 3, multi-center, double-blind, placebo controlled RCT, the ENVISION trial.

- The primary endpoint in ENVISION was annualized AIP attack rate, which was defined as an exacerbation that required hospitalization, urgent healthcare visit, or IV hemin administration.
- Subjects with greater than two attacks in the last six months were included in the trial.
- Only patients with the most common form of AHP; AIP, were included in the primary endpoint. In total, 5 patients with VP, HCP, or ADP were included in the trial, but excluded from this endpoint.
- In the ENVISION trial, givosiran reduced the absolute number of AIP attacks at six months as well as the use of rescue hemin as compared to placebo.
- The mean annualized AIP attack rate was 3.2 versus 12.5 attacks in the givosiran and placebo groups, respectively.
- The mean annualized days of hemin use in AIP patients was 6.77 versus 29.71 days in the givosiran and placebo groups, respectively.
- Daily worst pain score, using a validated pain scale, the Brief Pain Inventory- Short Form (BPI-SF), was assessed during the trial, as a key secondary endpoint. There was no statistically significant improvement in pain between the placebo and givosiran arms.

- Due to the short duration of the trial (6 months), it is unknown if givosiran will result in a clinically meaningful improvement in long-term QOL, overall survival, or a reduction in chronic complications (including hepatocellular carcinoma, chronic kidney disease, hypertension, or polyneuropathy).
- An interim analysis at month 24 of the long-term open-label extension of the ENVISION study showed continued benefit in patients that remained on givosiran, consistent with the double-blind period. [4]

Clinical Guidelines/Standard of Care Treatment [1]

- Recommendations published by the Porphyria Consortium advise of the following for the long-term management of AHP:
  * Education and avoidance of precipitating factors is key to prevention of AHP attacks.
  * Patients with recurrent attacks, defined as four or more attacks per year, are candidates for prophylactic hemin. However, hemin dosing and management is highly individualized.
  * The use of gonadotropin-releasing hormone (GnRH) analogues or switching to a low-dose hormonal contraceptive can prevent attacks in women with frequent luteal phase attacks.
  * Liver transplant in those with severe intractable attacks can provide benefit. However, due to the associated morbidity and mortality, transplant is considered a treatment of last resort.

Safety [5]

- During clinical trials the most frequent adverse events (>10% incidence) were nausea, injection site reactions, rash, serum creatinine increases, transaminase elevation, and fatigue.

Dosing [5]

- Givosiran is administered once monthly, in doses up to 2.5mg/kg/dose.
- Efficacy and dosing of givosiran in AHP patients in doses higher than 2.5mg/kg once monthly has not been established.

Cross References
Site of Care Review, Medication Policy Manual, Policy No. dru408

Codes	**Number**	**Description**
HCPCS	J0223	Injection, givosiran (Givlaari), 0.5 mg

Appendix 1: AHP Triggers[1]	
Medications (*see Appendix 2*)	Stress
Alcohol	Fasting
Smoking	Dieting
Infections or illnesses	Iron deficiency

Appendix 2: Unsafe medications in AHP [a][6]		
Anesthetics (etomidate, ketamine, thiopental)	Griseofulvin	Progesterone and synthetic progestins
Barbiturates	Hydralazine	Pyrazinamide
Carbamazepine	Hydroxyzine	Pyrazolones (aminopyrine and antipyrine)
Carisoprodol	Meprobamate	Rifampin
Clonazepam	Metoclopramide	Spironolactone
Danazol	Nifedipine	Succinimides (ethosuximide and methsuximide)
Diclofenac	Nitrofurantoin	Sulfasalazine
Efavirenz	Oxcarbazepine	Sulfonamide antibiotics
Ergots	Phenytoin	Tamoxifen
Estrogen	Phenobarbital	Topiramate
Glutethimide	Primidone	Valproic acid

[a] A complete and up-to-date list of unsafe medications can be found on the American Porphyria Foundation website https://porphyriafoundation.org/drugdatabase/

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Revision History

Revision Date	Revision Summary
6/20/2024	Addition of site of care requirement.
6/15/2023	No criteria changes with this annual update.
6/17/2022	No criteria changes with this annual update.
7/16/2021	No criteria changes with this annual update.
4/22/2020	New policy (effective 5/15/2020).

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Medication Policy Manual | **Policy No:** dru631

Topic: Reblozyl, luspatercept-aamt | **Date of Origin:** May 15, 2020

Committee Approval Date: June 20, 2024 | **Next Review Date:** 2025

Effective Date: September 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Reblozyl (luspatercept-aamt) is an injected medication used to treat certain types of anemias in patients who require regular red blood cell transfusions (RBCTs).

Policy/Criteria

Most contracts require pre-authorization approval of Reblozyl (luspatercept-aamt) prior to coverage.

I. Continuation of therapy (COT): Reblozyl (luspatercept-aamt) may be considered medically necessary for COT when criterion A, B, or C **AND** D below is met.

A. For diagnoses NOT listed in the coverage criteria below, full policy criteria must be met for coverage.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

AND

D. Site of care administration requirements are met [refer to Medication Policy Manual, *Site of Care Review*, dru408].

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Reblozyl (luspatercept-aamt) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A, B, and C below are met:

A. Site of care administration requirements are met [refer to Medication Policy Manual, *Site of Care Review*, dru408].

AND

B. Reblozyl (luspatercept-aamt) is prescribed by, or in consultation with a hematologist.

AND

C. Luspatercept will be used in one of the following settings when criterion 1 or 2 below are met:

1. A diagnosis of **beta thalassemia** when criteria (a and b) below are met.

a. Documented transfusion dependence, defined as transfusion of at least six units of packed red blood cells (PRBCs) in the previous 24 weeks.

AND

b. No transfusion-free period greater than 35 days (5 weeks) in the previous 24 weeks.

OR

2. A diagnosis of **myelodysplastic syndrome (MDS) with ring sideroblasts** when criteria (a, b, and c) below are met.

a. The MDS is classified as very low, low, or intermediate risk MDS according to the IPSS-R (see *Appendix 1*).

AND

b. Documented transfusion dependence, defined as transfusion of at least six units of packed PRBCs in the previous 24 weeks.

AND

c. Erythropoiesis-stimulating agents (ESA) treatment was ineffective, not tolerated, or is contraindicated (see *Appendix 2*).

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Reblozyl (luspatercept-aamt) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Reblozyl (luspatercept-aamt) may be approved in the following quantities:

1. Beta-thalassemia: Up to 1.25 mg/kg every 3 weeks.

2. MDS: Up to 1.75 mg/kg every 3 weeks.

C. Authorization **shall** be reviewed as follows to confirm that medical necessity criteria are met and that the medication is effective.

1. Initial authorization:

Beta-thalassemia: Authorization shall be reviewed after 18 weeks. If there is no documented decrease in transfusion burden after 18 weeks, no further Reblozyl (luspatercept-aamt) will be authorized for coverage.

NOTE: This time frame is based on response after 15 weeks (five doses) plus time to reassess the patient.

MDS: Authorization shall be reviewed after 24 weeks. If there is no documented decrease in transfusion burden after 24 weeks, no further Reblozyl (luspatercept-aamt) will be authorized for coverage.

NOTE: This time frame is based on response after 21 weeks (seven doses) plus time to reassess the patient.

2. Continued authorization (after the initial 18-week period): Authorization shall be reviewed annually.

3. <u>For all authorizations (initial and continued authorization)</u>: Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit evidenced by a reduction or sustained reduction in the need for PRBC transfusions (PRBCTs).

IV. Reblozyl (luspatercept-aamt) is considered not medically necessary when used in erythropoiesis-stimulating agent (ESA)-naïve transfusion-dependent MDS.

V. Reblozyl (luspatercept-aamt) is considered investigational when used for all other conditions.

Position Statement

Summary

- The intent of this policy is to allow for coverage of Reblozyl (luspatercept-aamt) in transfusion dependent patients with beta-thalassemia or lower-risk MDS, up to the doses shown to be safe and effective in clinical trials.
- *Beta-thalassemia:*
  * Evidence to support the use of Reblozyl (luspatercept-aamt) in beta-thalassemia was based on a phase 3, randomized, double-blind, placebo-controlled study in patients with beta thalassemia who required regular RBCTs. Reblozyl (luspatercept-aamt) reduced transfusion burden more than placebo. [1,2]
  * Current standard of care for patients with beta-thalassemia addresses the symptoms of the disease, primarily using life-long, ongoing RBCTs with additional iron chelation therapy to manage iron overload. [3]
- *MDS*:
  * The safety and efficacy of Reblozyl (luspatercept-aamt) was also evaluated in a phase 3, randomized, double-blind, placebo-controlled study in patients with very low, low, or intermediate risk MDS with ring sideroblasts who were dependent on RBCTs and unable to have treatment with ESAs. Patients treated with Reblozyl (luspatercept-aamt) needed less transfusions compared to patients treated with placebo. [4]
  * Subsequently, the FDA indication was expanded based on an open-label, comparative trial in ESA-naive transfusion-dependent anemia due to lower-risk MDS. [5] Despite an improvement in transfusion-independence with luspatercept as compared to epoetin, the clinical meaningfulness of the difference is uncertain. The trial included a higher percentage of patients with characteristics associated with better response to ESAs [lower baseline serum erythropoietin (sEPO), lower percentage of blasts, and low RBCT requirement]. Given the lack of clinical meaningful difference and the significantly higher cost of luspatercept relative to ESA therapy, the use of luspatercept in ESA-naïve transfusion-dependent MDS is considered 'not medically necessary.'

    * Guidelines by the NCCN recommend ESAs as first-line treatment for lower-risk MDS without ring sideroblasts, unless not a treatment option [such as in patients with a baseline serum erythropoietin (EPO) level over 500]. Luspatercept is listed as an option for MDS with ring sideroblasts. Other treatment options include chemotherapy (azacitidine, decitabine), targeted therapy (imatinib), immunosuppressive therapy (anti-thymocyte globulin, cyclosporine), and immunomodulators (lenalidomide). [6]

- In clinical trials, Reblozyl (luspatercept-aamt) doses were increased after six weeks (two doses) is there was suboptimal response, defined as no decrease in transfusion burden versus baseline. For the third dose (at week 9), the patient increased to the maximum dose of 1.25 mg/kg (beta-thalassemia) or 1.75 mg/kg (MDS). The majority of patients in clinical trials achieved a response within approximately four to five treatment cycles. After nine weeks of treatment at the maximum dose (after 15 weeks of treatment total), Reblozyl (luspatercept-aamt) is discontinued if there is no decrease in transfusion burden. Therefore, if a patient does not have a reduction in transfusion burden after 15 weeks of therapy, additional Reblozyl (luspatercept-aamt) may not be covered. [1,4,5,8]
- Reblozyl (luspatercept-aamt) may be covered for up to the doses shown to be safe and effective in the pivotal trials. The safety and effectiveness of higher doses have not been established.
- There is insufficient evidence to support the use of Reblozyl (luspatercept-aamt) in any other conditions.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy

Beta-thalassemia

- Safety and efficacy of luspatercept were evaluated in a phase 3, multicenter, randomized, double-blind, placebo-controlled trial in adult patients with beta-thalassemia who required regular RBCTs ("transfusion-dependent"). [2]
    * Patients were required to have received 6 to 20 RBC units within 24 weeks prior to the study and no transfusion-free periods of greater than 35 days.
    * Patients were randomized to receive 48 weeks of treatment with either luspatercept or placebo every 3 weeks. Treatments were administered in addition to best supportive care (BSC) which included RBCT and iron chelation therapy to maintain a patient's baseline hemoglobin level.
    * The primary endpoint was erythroid response defined as a ≥33% reduction from baseline in RBCT burden (with a reduction of ≥2 units).
    * Study results demonstrated a greater reduction in transfusion burden in patients treated with Reblozyl (luspatercept-aamt) compared to placebo.

MDS

- In patients with lower-risk MDS with ring sideroblasts, safety and efficacy of luspatercept were evaluated in a phase 3, multicenter, randomized, double-blind, placebo-controlled trial in patients who were refractory, intolerant, or ineligible for ESA treatment. [4]
    * Patients were required to have ≥2 RBC units in the previous 8 weeks and very low, low, or intermediate risk disease by the IPSS-R classification system.
    * Patients received treatment with Reblozyl (luspatercept-aamt) or placebo every 3 weeks.
    * The primary endpoint was RBC-transfusion independence (RBC-TI) ≥8 weeks between week 1 and 24, which was demonstrated in more patients in the luspatercept treatment group than in the placebo group.
- Subsequently, the FDA indication was expanded based on a published, phase 3, multicenter, randomized, open-label, comparative trial in patients with transfusion-dependent anemia due to lower-risk MDS and not previously treated with ESAs. [5]
    * The primary endpoint was RBC-transfusion independence (RBC-TI) ≥ 12 weeks AND a concurrent mean Hgb increase of at least 1.5 g/dL (between week 1 and 24), assessed in the intention-to-treat population.
    * All patients had:
        - Anemia due to very-low, low, or intermediate risk MDS [excluding MDS with del(5q)] [9% very low, 72% low]
        - Required 2–6 PRBC units per 8 weeks for ≥8 weeks immediately before randomization [median 3 RBCTs in prior 8 weeks* [63% with <4 RBCTs in 8 weeks)]
        - sEPO < 500 U/L [79% had sEPO <200].
        - No prior use of ESA.

* Patients were randomized to receive 24 weeks of open-label treatment: luspatercept or epoetin alfa, stratified by baseline transfusion burden (<4 units per 8 weeks vs ≥4 units per 8 weeks), endogenous serum EPO (≤200 U/L vs >200 to <500 U/L), and ring sideroblast status (positive vs negative). Of randomized patients, 73% with ring sideroblasts. Baseline Hgb 7.8 (7-8).
* Treatment was continued in patients with clinical benefit (defined as a transfusion reduction of ≥2 units RBCs per 8 weeks vs baseline) until evidence of disease progression, death, unacceptable toxicity, or withdrawal of consent.
* There was a statistically higher rate of transfusion-independence at 12 weeks with luspatercept (67%) as compared to epoetin (46%). However, the clinical meaningfulness of the difference in the reductions in RBCT burden or in RBC-TI between luspatercept and epoetin is unknown. Of note, the trial included a higher percentage of patients with characteristics associated with better response to ESA [sEPO <500, lower percentage of blasts, and pretreatment RBCTs <2/month ("low RBCT requirement")]. In addition, durability of response is also unknown. Given the lack of clinical meaningful difference and the significantly higher cost of luspatercept relative to ESA therapy, the use of luspatercept in ESA-naïve transfusion-dependent MDS is considered 'not medically necessary'.
* Although there is interest in the effect of biomarkers (ring sideroblasts or mutations such as SF3B1) on response to treatment of MDS-related anemia, the data from the exploratory analyses of these markers remain inconclusive as this study was not powered to establish cause and effect. Therefore, any associate of baseline mutations and response to either therapy remains unproven.
* Of note, the presence of ring sideroblasts is a favorable prognostic marker in MDS, whereas favorable response to ESAs is associated with baseline sEPO<500, lower percentage of blasts, and lower RBCT requirements at baseline. Because most subjects in this trial had ring sideroblasts (73%) and all had low sEPO (<500), the efficacy in ring-sideroblast negative ESA-naïve MDS-associated anemia is less clear.

- *Guidelines* [5]
  * Treatment goals for patients with lower-risk MDS include transfusion independence, improvement in hemoglobin levels, and maintenance of or improvement in quality of life.
  * For initial management of MDS-associated anemia, iron, folate, and B12 replacement are used in combination with RBCTs.
  * Erythropoiesis-stimulating agents (ESAs), epoetin alfa or darbepoetin, are a first-line medication treatment for anemia with lower-risk MDS, targeting early stages of erythropoiesis by inhibiting apoptosis and stimulating erythropoietin-responsive erythroid precursor proliferation (40-60% response rate). Lower baseline serum erythropoietin (sEPO) (<500), lower percentage of blasts, and lower pretreatment RBCTs (<2 per month) is associated with better response to ESAs. ESAs are dosed to a target Hgb of 10 to 12 g/dL (not to exceed 12). For lack

of efficacy with ESAs, dose escalation is recommended. After 6-8 weeks, treatment is stopped if ≤1.5 g/dL increase in Hgb or no reduction in RBCTs from baseline.

* Luspatercept (Reblozyl) is an option in anemic patients with ring sideroblasts if refractory to ESAs (or unlikely to respond to ESAs, namely those with sEPO above 500 at baseline).
* Other MDS-targeted options include chemotherapy (azacitidine, decitabine), targeted therapy (imatinib), immunosuppressive therapy (anti-thymocyte globulin, cyclosporine), and immunomodulators (lenalidomide).

Investigational Uses

- There is insufficient evidence to establish the efficacy of Reblozyl (luspatercept-aamt) for the treatment of other conditions, including non-proliferative chronic myelomonocytic leukemia, myelofibrosis, or non-transfusion dependent thalassemia. Data is limited to small, unpublished, phase 2 trials. Although the preliminary evidence is promising, larger, well controlled trials are needed to establish the safety and efficacy of Reblozyl (luspatercept-aamt) in these settings. Additional trials are ongoing. [7]

Safety [8]

- The most common adverse reactions associated with Reblozyl (luspatercept-aamt) include headache, bone pain, arthralgia, fatigue, cough, abdominal pain, diarrhea, and dizziness.

Dosing [8]

- The recommended dose of Reblozyl (luspatercept-aamt) in patients with beta thalassemia is 1 mg/kg (up to 1.25 mg/kg) every 3 weeks by subcutaneous injection. Safety and effectiveness of higher doses have not been established.
- In clinical trials of MDS, the dose of Reblozyl (luspatercept-aamt) was 1 mg/kg (up to 1.75 mg/kg) administered every 3 weeks by subcutaneous injection. The safety and effectiveness of higher doses have not been established.

Appendix 1: IPSS-R Prognostic Risk Categories/scores [9]	
Risk category	**Risk score**
Very low	≤ 1.5
Low	> 1.5 – 3
Intermediate	> 3 – 4.5
High	> 4.5 – 6
Very high	> 6

Appendix 2: Erythropoiesis-stimulating Agents (ESAs) [a]	
Aranesp	darbepoetin alfa
Epogen	epoetin alfa
Procrit	epoetin alfa
Retacrit	epoetin alfa-epbx

[a] For lack of efficacy with ESAs, dose escalation is recommended.[6]

Cross References
Site of Care Review, Medication Policy Manual, Policy No. dru408

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Revision History

Revision Date	Revision Summary
6/20/2024	No criteria changes with this annual review.
3/21/2024	Added the use in ESA-treatment-naïve transfusion-dependent MDS (a new FDA indication) as not medically necessary.
6/15/2023	No criteria changes with this annual update.
6/17/2022	No criteria changes with this annual update.
7/16/2021	No criteria changes with this annual update.
7/22/2020	Updated initial authorization periods to differentiate between beta-thalassemia and MDS and to be consistent with labeling.
4/22/2020	New policy (effective 5/15/2020). Limits coverage to patients with beta-thalassemia who require regular red blood cell transfusions. Coverage criteria also allows for patients with lower risk MDS who require regular red blood cell transfusions and are refractory, intolerant, or ineligible for ESA treatment, the settings in which luspatercept was studied.

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Medication Policy Manual | **Policy No:** dru632

Topic: Tepezza, teprotumumab | **Date of Origin:** May 15, 2020

Committee Approval Date: March 21, 2024 | **Next Review Date:** 2025

Effective Date: April 15, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Teprotumumab (Tepezza) is an infused medication used to treat thyroid eye disease. It is administered by a healthcare provider.

Policy/Criteria

Most contracts require pre-authorization approval of Tepezza (teprotumumab) prior to coverage.

I. Continuation of therapy (COT): Tepezza (teprotumumab) may be considered medically necessary for COT when criterion A or B plus criteria C **AND** D below is met.

A. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

OR

B. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

AND

C. The requested number of doses (infusions) is within the policy limits below.

PLEASE NOTE: Doses (infusions) already administered will be counted towards the coverable maximum quantity.

AND

D. Site of care administration requirements are met [refer to Medication Policy Manual, *Site of Care Review*, dru408].

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Tepezza (teprotumumab) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A through F below are met.

A. Site of care administration requirements are met [refer to Medication Policy Manual, *Site of Care Review*, dru408].

AND

B. A diagnosis of **Graves' disease**.

AND

C. Tepezza (teprotumumab) is prescribed by, or in consultation with an ophthalmologist.

AND

D. The patient has treated thyroid disease (normalized or normalizing) based on thyroid function testing, as defined by meeting one of the following criteria (1 or 2):

1. Normal thyroid function ("euthyroid"), defined as both thyroxine [T4] and triiodothyronine [T3] within normal limits of the lab.

OR

2. Normalizing thyroid function, defined as both T4 and free T3 levels less than 50% above OR 50% below normal limits of the lab.

AND

E. No prior surgical treatment for thyroid eye disease.

AND

F. Documentation of disease activity when criteria 1 or 2 below are met:

1. Significant (moderate to severe) symptoms of thyroid eye disease as defined by the following (a and b):

a. Clinical activity score (CAS) of at least 4 in at least one eye (see *Appendix 1*).

AND

b. The patient meets one of the following criteria (i, ii, or iii):

i. Presence of significant proptosis impacting daily life (attestation).

OR

ii. Presence of diplopia.

OR

iii. Treatment with an adequate course of intravenous glucocorticoids (IVGC) has been ineffective after at least 6 weeks, not tolerated, or is contraindicated

PLEASE NOTE: Standard dosing with IVGC consists of IV methylprednisolone (IVMP) at cumulative doses of 4.5 g over approximately 3 months (0.5 g weekly x 6 weeks followed by 0.25 g weekly for an additional 6 weeks.) A cumulative dose of IVMP > 8.0 g should be avoided.

OR

2. Stable/low to mild thyroid eye disease with proptosis as defined by the following (a. through c.):

a. Clinical activity score (CAS) of less than 4 in both eyes (see *Appendix 1*).

AND

b. Proptosis ≥3 mm above normal values for race and sex.

AND

c. The proptosis has resulted in a significant medical complication such as one of the following:

i. Diplopia

OR

ii. Eye pain due to proptosis

OR

iii. Documentation of inability to perform critical activities of daily living or demands of employment due to proptosis.

*PLEASE NOTE: Medical treatment of persistent proptosis is considered not medically necessary in the absence of significant medical complications associated with the condition. Treatment directed at improving the aesthetic appearance of proptosis alone does not qualify as a significant medical complication.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Tepezza (teprotumumab) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Tepezza (teprotumumab) will be approved for up to a total of eight infusions (one treatment course) per lifetime, based on dosing of up to a maximum of 20 mg/kg/dose every three weeks.

C. No additional doses beyond the maximum number of doses stated above will be authorized.

IV. The use of Tepezza (teprotumumab) for less severe thyroid eye disease without proptosis resulting in a significant medical complication is considered cosmetic. Use of Tepezza (teprotumumab) for cosmetic indications is considered not medically necessary and not coverable.

V. Tepezza (teprotumumab) is considered investigational when used for all other conditions, including but not limited to:

A. Diabetic macular edema.

B. Cutaneous systemic sclerosis.

C. Repeated treatment courses of Tepezza (teprotumumab).

Position Statement

Summary

- The intent of this policy is to allow for coverage of Tepezza (teprotumumab) in patients with thyroid eye disease (TED) due to Graves' disease, when lower-cost standard of care alternatives are not effective, up to the doses shown to be safe and effective in clinical trials (as detailed in the coverage criteria).
- Evidence to support the use of Tepezza (teprotumumab) in moderate to severe TED was based on two phase 3 trials. Patients included in the trials were required to have moderate to severe TED due to Graves' disease and treated thyroid disease (normalized

or normalizing). Previous treatment with Tepezza (teprotumumab), orbital irradiation, and/or surgery for thyroid eye disease was not allowed.

- Evidence to support the use of Tepezza (teprotumumab) in low-activity TED was established in one phase 4 trial in patients with stable or inactive disease, the presence of proptosis, and treated thyroid disease (normalized or normalizing). Those with previous treatment with Tepezza (teprotumumab) were excluded from the trial.
- Goals of treatment for TED include achieving a euthyroid state and symptom management. Overall, most patients with TED will benefit from supportive care with ocular lubrication and lifestyle modification.
- There are no clinical trials that compared the safety and efficacy of Tepezza (teprotumumab) over current first line treatment with intravenous glucocorticoids (IVGC). Therefore, the use of Tepezza (teprotumumab) before an adequate trial of IVGC is not coverable, unless a patient has diplopia or significant proptosis.
- The American Thyroid Association and European Thyroid Association TED guidelines state IVGC therapy is a preferred treatment for active moderate-to-severe TED when disease activity is the prominent feature in the absence of either significant proptosis or diplopia. Because available evidence for glucocorticoids shows negligible benefit for diplopia and proptosis, Tepezza (teprotumumab) is a preferred therapy for these patients. In patients with mild TED, watchful monitoring is recommended by the guidelines.
- There is insufficient evidence to support the use of Tepezza (teprotumumab) in any other conditions.
- Tepezza (teprotumumab) may be covered for up to the dose studied in clinical trials, as detailed in the coverage criteria.
- Clinical trials of multiple treatment courses (e.g., Optic X trial) are limited to small numbers of subjects with moderate to severe disease. Given the potential risk for permanent hearing impairment and intracerebral hemorrhage, there is insufficient data to establish the safety and effectiveness of higher or additional doses, included repeated treatment courses, have not been established. Therefore, the use of repeated treatment courses of Tepezza (teprotumumab) is considered investigational and not covered.

Disease Background *[1-3]*

- TED due to Graves' disease, also known as Graves' ophthalmopathy (GO), is a rare autoimmune condition caused by antibodies directed against receptors in the thyroid cells and on the surface of the cells behind the eyes. Muscles and fatty tissues behind the eye become inflamed, causing the eyes to be pushed forward and bulge outwards (proptosis). It can cause also cause eye pain, double vision, light sensitivity, or difficulty closing the eye.
- TED develops in approximately 40% of patients with Graves' disease, an autoimmune disease that causes hyperthyroidism. TED can occur in patients when their thyroid is overactive, underactive, or functioning normally. TED often improves on its own; however, in some patients, symptoms may persist despite treatment of the overactive thyroid gland.

- Tepezza (teprotumumab) may have a role in interfering with the receptors responsible for causing inflammation, pain, swelling, and other symptoms associated with TED.
- Goals of treatment in TED consists of achieving a euthyroid state and symptom management.
    * Initial treatment is for the underlying Graves' disease-related hyperthyroidism. Treatment options include medications [such as methimazole or propylthiouracil (PTU)], radioiodine therapy, and/or thyroid surgery.
    * The majority of patients with TED have mild-to-moderate disease. Supportive care with ocular lubrication (eyedrops and ointment), topical cyclosporine, and lifestyle modification (smoking cessation, sodium restriction, sunglasses) is the primary approach and sufficient for these patients.
    * Treatment for TED should start in the early months of the active inflammatory phase, as treatment becomes less effective as the disease progresses.

Clinical Guidelines [9]

- The American Thyroid Association and European Thyroid Association TED recently issued a consensus statement for the management of TED:
    * IVGC therapy is a preferred treatment for active moderate-to-severe TED when disease activity is the prominent feature in the absence of either significant proptosis or diplopia. Available evidence for glucocorticoids shows negligible benefit for diplopia and proptosis.
    * Standard dosing with IVGC consists of IV methylprednisolone (IVMP) at cumulative doses of 4.5 g over approximately 3 months (0.5 g weekly for 6 weeks followed by 0.25 g weekly for an additional 6 weeks). A cumulative dose of IVMP greater than 8.0 g should be avoided due to associated risk of severe hepatotoxicity.
    * Poor response to IVMP at 6 weeks should prompt consideration for treatment withdrawal and evaluation of other therapies.
    * Tepezza (teprotumumab) is a preferred therapy in patients with active moderate-to-severe TED with significant proptosis or diplopia based on clinical trials showing improvement in both symptoms.
    * In patients with mild TED, watchful monitoring is the preferred therapeutic option recommended by the guidelines. However, in patients with symptomatic inflammatory soft tissue involvement, oral glucocorticoids are an acceptable therapy.

Clinical Efficacy

- Tepezza (teprotumumab) is a human monoclonal antibody against the insulin-like growth factor-1 receptor inhibitor. Tepezza (teprotumumab) may interfere with the signaling pathway that mediates the symptoms associated with thyroid eye disease.
- In moderate to severe disease, the safety and efficacy of Tepezza (teprotumumab) were evaluated in two phase 3, multicenter, randomized, double-masked, placebo-controlled trials in patients with TED. [3,5-7]

    * Patients were required to have a diagnosis of Graves' disease with active, moderate-to-severe TED with significant symptoms, such as significant lid retraction, moderate or severe soft-tissue involvement, proptosis, and diplopia.
    * All patients had a CAS ≥4 and symptoms less than 9 months from the onset of thyroid eye disease.
    * All patients were euthyroid or with mild hypo- or hyperthyroidism.
    * Patients with previous orbital irradiation or surgery for TED were not allowed.
    * The primary endpoint in the first trial was a composite endpoint of reduction of ≥2 points in the CAS and a reduction of ≥2 mm in proptosis. The primary endpoint in the second trial was a reduction in proptosis of ≥2 mm. In both trials, significantly more patients treated with Tepezza (teprotumumab) demonstrated *less symptoms of TED than patients treated with placebo.*
- In stable disease/low clinical activity, the safety and efficacy of Tepezza (teprotumumab) were evaluated in one phase 4, multicenter, randomized, double-masked, placebo-controlled trial in patients with TED.[11]
    * Patients were required to have a diagnosis of TED with a CAS ≤1 in both eyes for at least one year or no additional inflammation or progression in proptosis/diplopia for at least one year.
    * All patients were also required to have proptosis of at least a 3 mm increase in proptosis before the diagnosis of TED and/or proptosis at least 3 mm above normal values for race and sex.
    * All patients were euthyroid or with mild hypo- or hyperthyroidism.
    * Previous treatment with Tepezza (teprotumumab) was not allowed.
    * The primary endpoint, reduction in proptosis measurement (mm), was significantly greater for patients in the Tepezza (teprotumumab) group compared with placebo.

Safety

- Data regarding retreatment with Tepezza (teprotumumab) is limited to 14 subjects enrolled in the Optic-X trial. Intracerebral hemorrhage was reported in 7.1% of study subjects, and hearing impairment was reported in 14.3%. There is insufficient safety data to support re-treatment with Tepezza (teprotumumab) at this time. [10]

Not Medically Necessary Uses

- There is no evidence to support the use of Tepezza (teprotumumab) in patients with less severe TED without proptosis. Clinical trials limited the patient population to patients with stable/inactive disease with proptosis or in patients with moderate to severe disease. Therefore, safety and efficacy in patients with less severe TED without proptosis have not been established. Therefore, the use of Tepezza (teprotumumab) for less severe thyroid eye disease without proptosis is considered not medically necessary and not coverable, given the lack of pain/functional impairment.

Investigational Uses

- There is insufficient evidence to establish the efficacy of Tepezza (teprotumumab) for any other conditions, including for the treatment of diabetic macular edema and cutaneous systemic sclerosis. Data is limited to small, early-stage trials. Well controlled trials are needed to establish the safety and efficacy of Tepezza (teprotumumab) in these settings. Trials are ongoing. [8]
- Repeated treatment courses:
  * Clinical trials of multiple treatment courses (e.g., Optic X trial) are limited to small numbers of subjects with moderate to severe disease. [10] Given the potential risk for permanent hearing impairment and intracerebral hemorrhage, there is insufficient data to establish the safety and effectiveness of higher or additional doses, included repeated treatment courses, have not been established. [7,9]
  * There is no evidence for the use of repeated treatment courses of Tepezza (teprotumumab) in patients with stable disease/low clinical activity.
  * Therefore, the use of repeated treatment courses of Tepezza (teprotumumab) is considered investigational and not covered.

Dosing [7]

- The recommended dose of Tepezza (teprotumumab) is 10 mg/kg for the first infusion, followed by 20 mg/kg every 3 weeks for 7 additional infusions (for a total of eight infusions for a single treatment course). The safety and effectiveness of higher doses or additional doses (or treatment course) have not been established.
- The use of repeated treatment courses of Tepezza (teprotumumab) is considered investigational (*see above section for more information*).

Appendix 1: Clinical Activity Score (CAS)	
The 7-point scale is comprised of 2 patient-reported outcomes and 5 clinician-reported outcomes. Each component is scored as present or absent, 1 or 0. The sum of these points is the total score, i.e., giving a range of 0-7, where 0 or 1 constitutes inactive disease and 7 severe active ophthalmopathy. A change of ≥2 points is considered clinically meaningful.	
1	Spontaneous orbital pain
2	Gaze evoked orbital pain
3	Eyelid swelling that is considered to be due to active Graves' ophthalmopathy
4	Eyelid erythema
5	Conjunctival redness considered due to active Graves' ophthalmopathy
6	Chemosis
7	Inflammation of caruncle or plica

Cross References
Site of Care Review, Medication Policy Manual, Policy No. dru408

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Revision History

Revision Date	Revision Summary
3/21/2024	Added coverage criteria for stable/low to mild TED with proptosis. In addition, added repeated treatment courses of Tepezza as investigational.
10/15/2023	Removed DMARD from step therapy requirements due to updated US/EU guidelines and evidence review. Kept step through IV glucocorticoids, unless member with diplopia or significant proptosis, which is in line with new US/EU guidelines.
3/18/2022	Clarified steroid step therapy requirement (IV steroids or oral steroids in combination with an oral csDMARD). No change to intent.
4/21/2021	Removed criterion requiring thyroid eye disease symptoms present for less than nine months; added Clinical Activity score in Appendix (effective 5/15/21).
7/22/2020	Updated criterion II ("New Starts") to read "A through G." No other changes to criteria.
April 22, 2020	New policy (effective 05/15/2020). Limits coverage to patients with moderate to severe thyroid eye disease when lower-cost standard of care alternatives are not effective.

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Medication Policy Manual

Policy No: dru633

Topic: Medications for pulmonary arterial hypertension (PAH)

Date of Origin: July 1, 2020

- Adempas (riociguat oral)
- ambrisentan oral (Letairis, generic)
- bosentan oral (Tracleer, generic)
- Opsumit (macitentan oral)
- Opsynvi (macitentan and tadalafil)
- Orenitram (treprostinil oral)
- Tyvaso, Tyvaso DPI (treprostinil inhalation)
- Uptravi (selexipag oral)
- Uptravi IV (selexipag injection)
- Ventavis (iloprost inhalation)
- Winrevair (sotatercept-csrk)

Committee Approval Date: June 20, 2024

Next Review Date: 2025

Effective Date: September 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

This policy is for medications used in the treatment of pulmonary arterial hypertension (PAH) and other specific forms of pulmonary hypertension.

Policy/Criteria

Most contracts require pre-authorization approval of medications for pulmonary arterial hypertension (PAH) prior to coverage.

I. Continuation of therapy (COT): Medications for PAH may be considered medically necessary for COT when criterion A, B or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1, 2, and 3 below must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

AND

3. **For branded bosentan (Tracleer) or branded ambrisentan (Letairis) only:** There is clinical documentation (including, but not limited to chart notes) of an intolerance or contraindication to an inactive ingredient in the generic equivalent medication (bosentan or ambrisentan).

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve): Medications for PAH (as listed in *Table 1*) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criterion A, B, or C below are met.

A. **Pulmonary arterial hypertension** (PAH) - Medications for PAH (as listed in *Table 1*), when criteria 1 and 2 below are met:

1. There is a diagnosis of **WHO Group 1 pulmonary arterial hypertension** (PAH) (see *Appendix I*). Note: This criterion is NOT met for patients with a diagnosis of pulmonary hypertension (PH), but group unspecified, or with the diagnostic workup ongoing.

AND

2. For the following medications only, specific criteria for PAH must also be met:

Medication	Criteria
• Opsumit (macitentan) • Opsynvi (macitentan and tadalafil) • Letairis (branded ambrisentan) • Tracleer (branded bosentan)	**i.** Generic bosentan and generic ambrisentan have been ineffective, not tolerated, or are contraindicated. **AND** **ii.** **For branded bosentan (Tracleer) or branded ambrisentan (Letairis) only:** There is clinical documentation (including, but not limited to chart notes) of an intolerance or contraindication to an inactive ingredient in the generic equivalent medication (bosentan or ambrisentan).
• Adempas (riociguat) • Uptravi (selexipag oral) • Orenitram (treprostinil oral)	**i.** Sildenafil or tadalafil have been ineffective, not tolerated, or are contraindicated. **AND** **ii.** Generic bosentan or generic ambrisentan have been ineffective, not tolerated, or contraindicated. **AND** **iii.** **For Orenitram (treprostinil oral)**: will be used as monotherapy.
Winrevair (sotatercept)	**i**. Will be used as **add-on** therapy: Documentation that the patient is currently being treated with a double or triple regimen of a**t least two** medications for PAH (as listed in *Table 1*) **AND** those PAH medications will be continued with Winrevair (sotatercept). **AND** **ii.** Persistent PAH: Documentation of WHO functional class (FC) II or III (see *Appendix III*).

OR

B. **<u>For Adempas (riociguat) only:</u>**

Pulmonary hypertension (PH) associated with chronic thrombotic and/or embolic disease (CTEPH) [WHO Group 4, see *Appendix II*], that is inoperable or with residual PH after pulmonary thromboendarterectomy (PTE).

OR

C. **<u>For Tyvaso (inhaled treprostinil) only:</u>**

Pulmonary hypertension (PH) associated with interstitial lung disease (PH-ILD) [WHO Group 3, see *Appendix II*] when there is documentation or attestation of diffuse parenchymal disease, based on lung imaging.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers all oral, inhaled, and subcutaneous medications for PAH coverable only under the pharmacy benefit (as self-administered medications).

B. Regence Pharmacy Services considers all intravenous (IV) medications for PAH coverable only under the medical benefit (as a provider-administered medication).

C. When pre-authorization is approved, medications for PAH will be authorized in quantities as listed in *Table 1*.

TABLE 1. Medications for Pulmonary Arterial Hypertension (PAH)

Product	Quantity Limit
Adempas (riociguat oral)	90 tablets per month
ambrisentan oral (Letairis, generic)	30 tablets per month
bosentan oral (Tracleer, generic)	60 tablets per month
Opsumit (macitentan oral)	30 tablets per month
Opsynvi (macitentan and tadalafil)	30 tablets per month
Orenitram (treprostinil oral)	not to exceed 42 mg per day
Tyvaso (treprostinil inhalation)	28 ampules (81.2 mL) per 28 days (one refill pack)
Tyvaso DPI (treprostinil inhalation)	up to dosing limits described in FDA-approved prescribing information
Uptravi (selexipag oral)	3,200 mcg per day (up to 1,600 mcg twice daily)
Uptravi IV (selexipag injection)	60 of the 1,800 mcg vials per month (up to 1,800 mcg twice daily)

<table>
<tr><td>Ventavis (iloprost inhalation)</td><td>540 ampules per month</td></tr>
<tr><td>Winrevair (sotatercept subcutaneous)</td><td><u>0.3mg/kg dose (initial dose):</u>
<table><tr><th>Weight</th><th>Quantity</th></tr><tr><td>158 kg or less</td><td>One 45 mg kit (one 45mg vial) per 21 days</td></tr><tr><td>Above 158kg</td><td>One 60mg kit (one 60mg vial) per 21 days</td></tr></table>
<u>0.7mg/kg dose (target dose):</u>
<table><tr><th>Weight</th><th>Quantity</th></tr><tr><td>67 kg or less</td><td>45mg kit (one 45mg vial) per 21 days</td></tr><tr><td>68-89 kg</td><td>60mg kit (one 60mg vial) per 21 days</td></tr><tr><td>90-132 kg</td><td>90mg kit (two 45 mg vials) per 21 days</td></tr><tr><td>133 kg and above</td><td>One 120mg kit (two 60mg vials) per 21 days</td></tr></table></td></tr>
</table>

D. Authorization:

1. For Winrevair (sotatercept) ONLY:

a. <u>Initial authorization</u> shall be limited to 6 months.

b. <u>Reauthorization</u> **shall** occur every 12 months thereafter with clinical documentation (including but not limited to chart notes) that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

2. Medications for PAH, except for Winrevair (as noted above) **may** be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

IV. Bosentan (Tracleer, generic) is considered not medically necessary when used for essential hypertension.

V. Uptravi IV (selexipag injection) is considered not medically necessary (for outpatient use).

VI. Medications for PAH are considered investigational when used for all other conditions, unless specified above in the coverage criteria, including but not limited to:

A. All other types of pulmonary hypertension (PH) [WHO Groups 2-5, see *Appendix II*], including PH associated with the following (unless specified above in the coverage criteria):

1. Left heart disease, including congestive heart failure (CHF) [WHO Group 2].

2. Lung diseases, including chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF) [WHO Group 3] except as noted in the coverage criteria.

3. Miscellaneous causes, such as sarcoidosis (WHO Group 5).

B. **Specific oral therapies [Opsumit (macitentan), Opsynvi (macitentan and tadalafil), Adempas (riociguat), Uptravi (selexipag oral), Orenitram (treprostinil oral) only]:** Digital ischemia and/or ulcers, including Raynaud's phenomenon, due to systemic sclerosis, scleroderma, or other causes.

C. **Ambrisentan (Letairis, generic), Opsumit (macitentan), Opsynvi (macitentan and tadalafil), bosentan (Tracleer, generic), and Adempas (riociguat) only:** Idiopathic pulmonary fibrosis (IPF), with or without pulmonary hypertension.

D. **Adempas (riociguat) only:** Use in combination with any phosphodiesterase inhibitor, including sildenafil (generic Revatio), tadalafil (generic Adcirca), dipyridamole, or theophylline.

E. **Bosentan (Tracleer, generic) only:** Behçet's disease.

F. **Orenitram (treprostinil oral) only:** Use in combination with other PAH-specific medications, including all medications listed in Table 1, as well as sildenafil, tadalafil, epoprostenol injection, and treprostinil injection.

G. **Winrevair (sotatercept subcutaneous) only:** Use as monotherapy or in WHO Functional class I or IV or in treatment naive patients with PAH.

Position Statement

Summary

- The intent of this policy is to cover medications for PAH for the indications and dose for which they have been shown to be safe and effective, as detailed in the coverage criteria:
  * WHO Group 1 pulmonary arterial hypertension (PAH), when treatment with lower cost generic therapies are ineffective or not a treatment option.
  * Adempas (riociguat) only: Group 4 pulmonary hypertension (PH) associated with chronic thrombotic and/or embolic disease (CTEPH), when pulmonary thromboendarterectomy (PTE) is ineffective or not a treatment option.
  * Tyvaso (treprostinil inhalation) only: Group 3 pulmonary hypertension (PH) associated with interstitial lung disease (ILD), with diffuse parenchymal disease, based on lung imaging.

* Winrevair (sotatercept) only: as add-on therapy for persistent PAH (functional class II/III), despite current double or triple background PAH regimens.

- *Pulmonary Arterial Hypertension (PAH)*
  * There is insufficient evidence to establish any one oral therapy for PAH is clearly superior to another. Generic sildenafil is the lowest-cost oral medication for PAH and a treatment option for most treatment-naïve PAH patients, along with generic tadalafil, both phosphodiesterase-5 inhibitors (PDE5is).
  * Among the endothelin receptor antagonists (ERAs), generic ambrisentan and generic bosentan are the lowest cost. There is no evidence that any one ERA is safer or more effective than another. However, among the medications for PAH with an available generic product, including ambrisentan and bosentan (see *Table 1*), the generic product is the lower cost option. Therefore, the branded products are covered only when the generic equivalent is not a treatment option.
  * Injectable prostanoids epoprostenol and treprostinil are available as lower-cost generic options. The branded prostanoids (prostacyclin analogues or PCAs) for PAH [Ventavis (iloprost inhalation), Tyvaso (treprostinil inhalation), and Orenitram (treprostinil oral)] have been studied individually in the treatment of PAH. To date, there is insufficient evidence that any one of these products is safer or more effective than the other.
  * The addition of Orenitram (treprostinil oral) to other PAH-specific medications, such as oral phosphodiesterase-5 inhibitors (PDE5is) or endothelin-receptor antagonists (ERAs), has not been shown not improve exercise tolerance over monotherapies for PAH. [1 2]
  * New therapies [Adempas (riociguat), Uptravi (selexipag oral) and Orenitram (treprostinil oral)] are coverable when low-cost generics are not an option, given the lack of superiority to lower cost oral step therapy options, as well as lower cost generic PCAs. Adempas (riociguat) and Uptravi (selexipag oral) have been studied when used for PAH inadequately managed with oral PDE-5is and ERAs.
- *Other Coverable Pulmonary Hypertension Uses*
  * For pulmonary hypertension due to CTEPH, surgical clot removal with pulmonary thromboendarterectomy (PTE) is the treatment of choice and standard of care therapy. PAH-specific medication therapies may be considered for patients unable to have surgery or with residual PH; however, the evidence for efficacy is limited. All CTEPH patients should receive along with lifelong anticoagulation. [3] Adempas (riociguat) has been FDA-approved for and may be a treatment option for inoperable or recurrent CTEPH. Other PAH medications are being studied for use in CTEPH; however, there is insufficient evidence at this time to support the use of any other PAH medications for this indication.
  * Pulmonary hypertension (PH) due to interstitial lung disease (PH-ILD) is a specific type of PH associated with fibrotic lung disease. Tyvaso (treprostinil inhalation) has been FDA-approved for and may be a treatment option for PH-ILD. Other PAH medications are being studied for use in PH-ILD; however,

there is insufficient evidence at this time to support the use of any other PAH medications for this indication.

- The World Health Organization (WHO) classifies pulmonary hypertension (PH) in five groups, based on underlying etiology of PH. [4]
  * Group 1 (pulmonary arterial hypertension) patients have generally irreversible, progressive disease and may require treatment with PAH-specific therapies.
  * For patients with Groups 2-5, PH may be reversible. Therapy should be directed at treating the underlying cause, such as clot removal for PH due to chronic thromboembolic (CTEPH) with pulmonary thromboendarterectomy (PTE). For pulmonary hypertension due to lung disease (Group 3 PH), the underlying lung disease should be treated, along with supportive therapies. [4 5]
- Pharmacologic treatment of PAH includes oral anticoagulants, diuretics, oxygen, inotropic agents (digoxin and dobutamine), calcium channel blockers, prostacyclin, and prostacyclin analogs (PCAs) [epoprostenol, treprostinil (generic Remodulin, Tyvaso), Ventavis (iloprost), and Uptravi (selexipag)], endothelin-receptor antagonists (ERAs) [ambrisentan, bosentan, Opsumit (macitentan), Opsynvi (macitentan and tadalafil)], PDE-5 inhibitors (PDE5is) (sildenafil, tadalafil), the soluble guanylate cyclase stimulator (sGCs) Adempas (riociguat), and the activin signaling inhibitor Winrevair (sotatercept SC).
- For the treatment of PAH, a stepwise approach is generally used to manage patients. In early disease or with less severe symptoms, oral therapies are used. As symptoms progress, inhaled or injectable therapies, such as epoprostenol injectable, iloprost inhaled and treprostinil injectable/inhaled may be used [4]
- Medications for PAH may be covered at the doses been shown to be effective (as detailed in the coverage criteria). There is no insufficient evidence that doses of medications for PAH exceeding those listed in the coverage criteria provide any additional clinical benefit when used in the treatment of coverable indications.
- There is currently insufficient evidence, except as noted in the efficacy section below, for ambrisentan, bosentan, Ventavis (iloprost inhalation), Uptravi (selexipag oral), or Orenitram (treprostinil oral) in patients with Groups 2-5 PH. In addition, medications for PAH may be harmful in some situations and raises the overall cost of care.
- The pivotal PAH trial of Adempas (riociguat) allowed use in combination with bosentan or inhaled prostanoids (PCAs). However, use of Adempas (riociguat) with any phosphodiesterase-5 inhibitor (e.g., sildenafil, tadalafil, dipyridamole, theophylline) is contraindicated due to excessive hypotension in combination.

Clinical Efficacy

- Medications for PAH are used for the treatment of pulmonary arterial hypertension (PAH), Adempas (riociguat) for both PAH and CTEPH, and Tyvaso (treprostinil inhalation) for both PAH and PH-ILD to improve exercise ability, symptoms and time to clinical worsening. [6]
- For the covered indications, medications for PAH were found to improve performance on the 6-minute walk test, as well as symptoms (functional class) relative to placebo. The

six-minute walk test (6MWD) is a measure of exercise tolerance and measures the distance that is covered in a 6-minute timeframe. Improvements in this test have been correlated to improved survival in PAH patients. WHO functional class is a measure of activity level and correlated with disease severity and outcomes but can be prone to reporting bias.

The 6MWD is the standard used by the FDA for the approval of new drugs in the treatment of PAH; however, the clinical relevance of less than a 10% improvement in 6MWD is not known.

Endothelin receptor antagonists (ERAs)

- *Ambrisentan (generic, Letairis):* In two reliable pivotal randomized, controlled studies in adults with PAH found ambrisentan improved exercise capacity at 12-weeks, based on the six-minute walk test compared to placebo. [7 8]
- *Bosentan (generic, Tracleer):* In four unreliable randomized, controlled studies adults with PAH found bosentan may improve ability to exercise at 16-24 weeks based on 6MWD compared to placebo.[9-12] All of the studies were significantly flawed, due to short trial duration, incomplete reporting of results, high dropout rates, and use of a non-clinical primary endpoint (pulmonary vascular resistance index).
- *Opsumit (macitentan):* In one low confidence randomized, controlled study, in adults with PAH, Opsumit (macitentan) reduced occurrence of the primary endpoint compared to placebo. [13] The primary composite endpoint was time to death, a significant morbidity event or worsening of PAH (symptoms or the need for additional treatment). Significant events were defined as atrial septostomy, lung transplantation, or initiation of injectable prostacyclin and prostacyclin analogs (PCAs).
    * The majority of the benefit was in reduction in percentage of patients with PAH clinical worsening (-12.8% placebo-subtracted), which includes measurement of 6MWD. Effect on the rate of death and need for PCA therapy was small (absolute difference -0.2% and -2%). The trial was not powered for reduction of mortality, the most meaningful outcome for PAH.
    * Significant flaws in the trial included assessment bias for morbidity events, moderately high attrition and inclusion of few patients from North America. [14]
    * There are no head-to-head studies of Opsumit (macitentan) with other PAH therapies. However, 64% of the patients in the pivotal trial continued on stable doses of PAH medications (61% PDE5is; 6% oral or inhaled PCAs). Opsumit (macitentan) has not been studied in combination with injectable PCAs [e.g., epoprostenol or treprostinil subcutaneous].

Combination Products

- *Opsynvi (macitentan and tadalafil):* The approval of Opsynvi (macitentan and tadalafil) was based on efficacy and safety data from studies to support the approval of Opsumit (macitentan) and Adcirca (tadalafil) individually. In an additional phase 3 trial including 187 patients with PAH, either treatment naïve or on background ERA or PDE5i therapy, Opsynvi (macitentan and tadalafil) demonstrated a 28% reduction in pulmonary artery resistance (PVR) compared to each macitentan or tadalafil

monotherapy alone.[15 16] However, no studies have compared Opsynvi (macitentan and tadalafil) to a combination of Opsumit (macitentan) + tadalafil or any other ERA+PDE5i combination treatment; therefore, any difference in efficacy or safety between the combination product, Opsynvi (macitentan and tadalafil), and a combination of its individual components as separate products, is unknown. Soluble guanylate cyclase stimulator (sGCs)

- *Adempas (riociguat)*: The efficacy and safety of riociguat was evaluated in two published randomized, double-blind, placebo-controlled trials in both CTEPH (n =261) and PAH patients (n = 443). The primary endpoint for both trials was improvement in exercise capacity, as measured by six minute walking distance (6MWD), a validated surrogate marker for PH treatment response. [17 18]
  * CTEPH: [17]
    - All enrolled patients were ineligible for or had PH refractory to surgical clot resection (pulmonary endarterectomy).
    - Adempas (riociguat) was superior to placebo for improvement in 6MWD at 16 weeks (+ 46 meters (m), placebo-adjusted; mean baseline 347 m). In addition, symptoms (functional class) improved more frequently (33% vs. 15% placebo).
    - There are no trials of Adempas (riociguat) for CTEPH in combination with any other PAH medications.
  * PAH: [18]
    - The pivotal trial enrolled both patients naïve to PAH-specific therapy as well as those stable on PAH-specific medications, including ERAs or prostanoids (n=443).
      - Patients on PDE-5is were excluded, given the risk of hypotension when used with Adempas (riociguat). The majority of randomized patients (50%) were previously treated with an ERA or PCA and continued on therapy (44% bosentan, 6% non-intravenous PCA).
      - Adempas (riociguat) 2.5 mg three times daily was superior to placebo for improvement in 6MWD at 12 weeks (+ 36 m, placebo-adjusted; mean baseline 363 m). In addition, symptoms improved more frequently (21% vs. 14% placebo) and time to clinical worsening delayed.
    - Subsequently, an open-label switch trial evaluated transition of patients with uncontrolled PAH symptoms on PDE-5 inhibitor (PDE5i) therapy to riociguat, as compared to continuation of baseline PDE-5 inhibitor therapy (n=226) [REPLACE]. [19] Of note, 71% of randomized patients were on both PDE-5 inhibitor (PDE5i) and ERA therapy at baseline.
    - There is insufficient evidence to establish that Adempas (riociguat) is superior to PDE-5i or ERA therapy for PAH. Most patients in clinical trials were previously treated with a PDE-5i and/or ERA therapy. [18 19]

Therefore, Adempas (riociguat) for PAH is coverable only after step therapy with both PDE-5i and ERA therapy.

Prostacyclin, and prostacyclin analogs (PCAs) (epoprostenol, treprostinil, iloprost, and selexipag)

- *Injectable PCAs (epoprostenol, treprostinil injection):* Pivotal trials for PAH suggested improvement in exercise capacity based on the 6MWD compared to placebo. [20 21]
- *Ventavis (iloprost inhalation):*
  * One published randomized study compared Ventavis (iloprost inhalation) to placebo. The pivotal reliable placebo-controlled study found Ventavis (iloprost inhalation) improved PAH symptoms, based on exercise tolerance (by ≥ 10%) measured using 6MWD and improvement in New York Heart Association (NYHA) functional status class (composite endpoint). The trial was only 12 weeks duration.
  * Two unreliable trials of Ventavis (iloprost inhalation) as add-on therapy in adults with PAH who remain symptomatic on bosentan had mixed results. Ventavis (iloprost inhalation) improved exercise capacity at 12-weeks based on the 6MWD compared to placebo in one trial. [22] A second trial was terminated early for lack of clinical benefit. [12]
- *Tyvaso (treprostinil inhalation):* The efficacy and safety of Tyvaso (treprostinil inhalation) was evaluated in two randomized, double-blind, placebo-controlled trials in both PH-ILD (n =326) and PAH (n = 235). [23 24] The primary endpoint for both trials was improvement in exercise capacity, as measured by 6MWD, a validated surrogate marker for PH treatment response.
  * PAH: Tyvaso (treprostinil inhalation) improved PAH symptoms based on exercise tolerance measured using 6MWD and quality of life in patients who remained symptomatic on bosentan or sildenafil; however, no other secondary endpoints were statistically significantly improved, such as time to clinical worsening, dyspnea, functional status, and other PAH signs and symptoms. The study was significantly flawed including excessive differential dropout rate between treatment arms (5.7%) combined with low overall completion rate of 86%, and short trial duration (only 12 weeks).
  * PH-ILD: Tyvaso (treprostinil inhalation) improved exercise tolerance using 6MWD; however, there is a lack of long-term data as well as evidence for improvement on overall quality of life and mortality. In addition, several study flaws, including the heterogeneity of ILD types in the clinical trial make it difficult to identify patients who would benefit most.
- *Orenitram (treprostinil oral):*
  * In one low-confidence randomized, controlled study in adults with PAH: [25]
    - The trial enrolled only patients naïve to PAH-specific therapy, as initial trials found no benefit from use of Orenitram (treprostinil oral) as add-on therapy.

- Orenitram (treprostinil oral) up to 12 mg twice daily modestly improved 6MWD compared to placebo. The mean dose at week 12 was 3.4±1.9 mg twice daily.
- However, the trial was not powered for reduction of mortality, the most meaningful outcome for PAH. This limited duration trial with a modest change in a surrogate endpoint provides little information about long-term treatment benefit.
- The study was significantly flawed, including a significant loss of the intent-to-treat population, moderately high attrition, differential loss, and a protocol amendment post-randomization.

* There is insufficient evidence to establish that Orenitram (treprostinil oral) is superior to PDE-5i or ERA therapy for PAH. There are no head-to-head studies of Orenitram (treprostinil oral) with other PAH therapies. Therefore, Orenitram (treprostinil oral) for PAH is coverable only after step therapy with both PDE-5i and ERA therapy.
* Orenitram (treprostinil oral) has not been proven effective as add-on therapy to other PAH-specific medications. In two Phase 3 trials, addition of Orenitram (treprostinil oral) did not significantly increase 6MWD in patients on a PDE5i, ERA, or both as compared with placebo (10 to 11 meters more than placebo). [1 2] A third combination therapy study protocol was withdrawn, prior to trial enrollment. [26]

- *Uptravi (selexipag oral):*

* The efficacy of Uptravi (selexipag oral) was initially established as add-on therapy for PAH. In the pivotal randomized, controlled study of adults (n=1,156) with previously treated PAH, Uptravi (selexipag oral) up to 1,600 mcg twice resulted in a 40% reduction in the occurrence of the primary endpoint compared to placebo. [GRIPHON] [27]
  - The trial enrolled both patients naïve to PAH-specific therapy as well as those stable on PAH-specific medications. The majority of randomized patients (80%) continued on stable doses of PAH medications (15% ERAs, 32% PDE5is; both 33%).
  - The primary composite endpoint was time to death, a significant morbidity event or disease progression (symptoms or the need for additional treatment). Significant events were defined as hospitalization, atrial septostomy, lung transplantation, or initiation of injectable prostacyclin/prostacyclin analogs (PCAs) or long-term oxygen. Disease progression was defined as a 15% decrease in 6MWD accompanied by a worsening in WHO functional class or the need for additional treatment of PAH.
  - The majority of the benefit was in reduction in percentage of patients with hospitalization (-4.9% placebo-subtracted) and PAH clinical worsening (-10.6% placebo-subtracted), which includes measurement of 6MWD.

- Effect on the rate of death and need for PCA therapy was small (absolute difference -1.8% and -0.5%). The trial was not powered for reduction of mortality, the most meaningful outcome for PAH.
- The study was significantly flawed including assessment bias for morbidity events, moderately high attrition (19%), high differential attrition between treatment arms (> 5%), and inclusion of few patients from North America.

* Subsequently, one small (n=34) open-label, observational (single-arm) switch trial evaluated transition of patients with stable PAH symptoms on Tyvaso (treprostinil inhalation) to Uptravi (selexipag oral) [TRANSIT-1]. [28]
  - All patients were on at least one baseline oral PAH therapy (PDE-5i ERA, and/or sGC). Notably, 56% of patients were on both PDE-5i and ERA therapy.
  - The trial did not compare Uptravi (selexipag oral) with any other therapies to allow any conclusion regarding comparative safety or efficacy.
* There is insufficient evidence to establish that Uptravi (selexipag oral) is superior to any other medication for PAH. There is insufficient data from head-to-head studies of Uptravi (selexipag oral) with other PAH therapies to establish superiority over other treatment options, including PDE-5is, ERAs, or other PCAs, as add-on therapy or as initial therapy.
  - Most patients in the available clinical trials were previously treated with PDE-5i and/or ERA therapy. [27 28] Therefore, Uptravi (selexipag oral) for PAH is coverable only after step therapy with both PDE-5i and ERA therapy.
  - One comparative RCT of double- versus triple-therapy in treatment-naïve patients with PAH compared PDE-5i/ERA (tadalafil, macitentan) with or without Uptravi (selexipag oral) [TRITON].[29] Both regimens were effective, but neither superior. Therefore, superiority of Uptravi (selexipag oral) remains unproven. A subsequent phase 4 trial found no difference in daily activity levels with addition of Uptravi (selexipag oral) to stable PDE-5i/ERA therapy. [30]

- Uptravi (selexipag oral) has not been studied in combination with other PCAs. One trial compared switch therapy from Tyvaso (treprostinil inhalation) to Uptravi (selexipag oral), but not combination therapy (detailed above). [28] The TRITON combination therapy trial did not include combination therapy with other PCAs (detailed above). [29]

Uptravi IV (selexipag injection)

- Subsequently, Uptravi IV (selexipag injection) was approved for short-term use in patients with PAH who were established and stable on Uptravi (selexipag oral). The approval was based on results from a small switch trial (n=20). The primary outcome for the 3-day trial was safety.[31]

- Use of Uptravi IV (selexipag injection) is considered "not medically necessary" for use in the outpatient setting and is not coverable for outpatient use.
    * All patients enrolled in the Uptravi IV (selexipag injection) trial were hospitalized for the IV infusions.
    * The FDA label specifies for use "in patients who are temporarily unable to take oral therapy." It is not labeled for self-administration or long-term use.

Activin Signaling Inhibitors

Winrevair [sotatercept subcutaneous (SC)]

- The available evidence for efficacy and safety of Winrevair (sotatercept SC) is limited to one pivotal phase 3, randomized, placebo-controlled trial in patients with persistent PAH despite current PAH-specific therapy (n=323). [32]
    * All enrolled patients had a confirmed diagnosis of PAH and documented persistent PAH symptoms, with a WHO functional class II or III, despite stable PAH-specific therapies.
    * Patients were on stable background double or triple standard of care PAH-specific therapies. Winrevair (sotatercept SC) or placebo were started as add-on therapy to the double/triple PAH-specific therapy regimens.
    * The primary endpoint was the change from baseline at week 24 in the 6MWD, a validated measure of functional capacity and symptomatic improvement in daily activities in PAH patients. The primary endpoint favored Winrevair (sotatercept SC) over placebo with a difference of 40.8 meters in 6MWD (95% CI 28 to 54, $p<0.001$).
- The safety and efficacy of Winrevair (sotatercept SC) in settings other than those studied in the pivotal trial are unknown, including the following:
    * In treatment-naïve patients.
    * As monotherapy.
    * In less/more severe PAH (WHO functional classes I or IV).
    * In other types of pulmonary hypertension (WHO Group 2-5).
- At this time, there is no evidence to compare the safety or efficacy of add-on therapies for persistent PAH (patients on ≥ 2 PAH-specific therapies), including add-on Winrevair (sotatercept SC) versus standard of care add-on prostacyclin/prostacyclin analogs (e.g. injectable epoprostenol or treprostinil), which have years of safety and efficacy experience. However, Winrevair (sotatercept) is significantly higher cost as compared to usual dosing of treprostinil injection or epoprostenol injection. Therefore, as aligned with the available clinical trial evidence, Winrevair (sotatercept) is coverable only as add-on therapy in patients with persistent PAH (FC II/III) despite current regimens of ≥ 2 PAH-specific therapies.

Guidelines

- Pulmonary arterial hypertension guidelines from the 2019 CHEST Guideline and Expert Panel Report [33]
    * Guidelines recommend the use of medications for PAH in WHO Group 1 PAH (see Appendix I) based on systematic review of the literature.
    * Graded recommendations and ungraded consensus statements for specific therapy are rated based on the available evidence.
    * For treatment-naïve individuals with WHO functional class (FC) I, continued monitoring is recommended for the development of symptoms what would signal disease progression and warrant initiation of pharmacotherapy (ungraded consensus-based statement).
    * For treatment-naïve PAH patients with WHO functional class (FC) II/III:
        o For individuals who are willing or able to tolerate combination therapy, a recommendation for combination therapy with ambrisentan and tadalafil is listed (weak recommendation, moderate quality evidence). For individuals unwilling or unable to tolerate combination therapy, a recommendation for monotherapy with either bosentan, macitentan, ambrisentan, riociguat, sildenafil, or tadalafil is listed, with no specific preference for one monotherapy agent over another.
    * For PAH patients with WHO FC IV symptoms and select WHO FC III (with rapid disease progression or poor prognostic markers) initial therapy with an injectable prostacyclin analog is listed, based on consensus. Inhaled or injectable prostacyclin may be added for WHO FC III patients with progressive symptoms despite one or two classes of oral PAH medications.
    * For uncontrolled PAH FC III/IV, step-wise approach to add-on therapy is advised, with most suggested therapies based on consensus statement.
    * Guidelines have not been updated since the approval of Winrevair (sotatercept).
- For suspected PH due to interstitial lung disease (PH-ILD), a specific subset of PH due to lung disease (PH Group 3), guidelines recommend: [4]
    * Management approach includes optimal treatment of the fibrotic lung disease and supportive therapies when indicated (e.g., oxygen, diuretics).
    * Additionally, referral to pulmonary rehabilitation and evaluation for lung transplantation are recommended in appropriate cases.
    * Of note: guidelines for PH Group 3 (2009) have not been updated since the approval of Tyvaso (treprostinil inhalation) for PH-ILD.
- Management of CTEPH consensus statement (ISHLT): [34]
    * Medications for PAH, including sildenafil, bosentan, Adempas (riociguat), and treprostinil injection, have been studied in CTEPH patients who are not candidates for surgery [pulmonary thromboendarterectomy (PTE)] and those with residual PH after PTE. However, Adempas (riociguat) remains the only FDA-approved agent for inoperable or residual/recurrent CTEPH following PTE.

    * There is currently no evidence to support using targeted PH therapy before PTE in patients with operable CTEPH, meaning use prior to (or in lieu of) surgery.

Safety

- Ambrisentan (generic, Letairis), bosentan (generic, Tracleer), Opsumit (macitentan), Opsynvi (macitentan and tadalafil), and Adempas (riociguat) are only available through a Risk Evaluation and Mitigation Strategy (REMs) program, to education patients about the risks fetal toxicity and ensure they are not used in pregnant women, due to the risk of fetal harm. The bosentan (generic, Tracleer) REMs program also requires monitoring for liver dysfunction. [35]
- Coadministration of phosphodiesterase (PDE) inhibitors, including specific PDE-5 inhibitors (such as sildenafil, tadalafil, or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline), with Adempas (riociguat) is contraindicated, due to additive hypotension leading to a high rate of discontinuation. [6] In addition, there was one death possibly related to the combination of riociguat and sildenafil. Warnings and precautions for Winrevair (sotatercept SC) include increased hemoglobin levels, thrombocytopenia, bleeding risk (mainly epistaxis and gingival bleeding) and telangiectasia. [36]

Investigational Uses

- Guidelines do not support the use of PAH medications for treatment of pulmonary hypertension (PH) in WHO Groups 2-5 (unless noted above), including PH related to chronic left heart disease (WHO Group 2) or chronic hypoxic states (WHO Group 3). Instead, these patients require optimization of therapies targeting their underlying disease state. [4]
- Raynaud's phenomenon: [26]
    * Trials of Adempas (riociguat) in Raynaud's phenomenon, for improvement of digital blood flow, are ongoing. Adempas (riociguat) was not found to significantly improve modified Rodnan skin scores (mRSS) versus placebo in patients with systemic sclerosis (SSc).[37]
    * Uptravi (selexipag oral) had no benefit over placebo in reducing the frequency of Raynaud's phenomenon attacks related to systemic sclerosis (SSc) in one placebo-controlled trial.[38]
    * Orenitram (treprostinil oral) is being studied in patients with digital ulcers and/or digital ischemia related to Raynaud's phenomenon, systemic sclerosis (SSc), or scleroderma, to improve peripheral blood flow and reduce digital ulcers. Results are not yet available. [26 39 40]
- Idiopathic pulmonary fibrosis (IPF):
    * The use of ambrisentan (generic, Letairis) is contraindicated in patients with IPF. [6] A placebo-controlled trial in patients with idiopathic pulmonary fibrosis (IPF), with or without pulmonary hypertension (WHO Group 3), found ambrisentan increased the risk of disease progression or death versus placebo.

    * One placebo-controlled study of bosentan (generic, Tracleer) in patients with idiopathic pulmonary fibrosis (IPF) (n=158) found no significant difference between bosentan and placebo treatment based on improvement in exercise capacity (6-minute walk distance).[41] A subsequent larger trial failed to demonstrate delays in IPF worsening or death with bosentan.[42]
    * A phase 2b placebo-controlled study of Adempas (riociguat) in patients with IPF was terminated early due to an increased number of deaths and no benefit for 6MWD. [43]
    * A phase 2b placebo-controlled study evaluated sildenafil as add-on therapy to Esbriet (pirfenidone) in patients with IPF. There was no benefit with sildenafil for the composite primary endpoint (disease progression and all-cause mortality).[44]

- Valvular heart disease: Use of sildenafil in patients with persistent pulmonary hypertension after valvular heart disease surgery [PH related to chronic left heart disease (WHO Group 2)] was associated with worse outcomes as compared to placebo. [45]
- CTEPH: One small (n=28) phase 2 trial of Uptravi (selexipag oral) for CTEPH failed to meet the primary endpoint [change in pulmonary vascular resistance (PVR)]. [46] A subsequent larger (n=78) phase 2 trial met the primary endpoint of PVR, but not the secondary health outcomes of 6MWD and WHO functional class. [47]
- Behçet's disease: One small randomized, placebo-controlled trial (n=10) found no reduction in disease activity with bosentan (Tracleer, generic) in patients with Behçet's disease.[48]

Cross References
BlueCross BlueShield Association Medical Policy, 5.01.09 - Advanced Therapies for Pharmacologic Treatment of Pulmonary Hypertension. [December 2022]

Appendix I: Revised World Health Organization (WHO) Classification of pulmonary hypertension (PH) – Group 1 [4]

Group 1. Pulmonary arterial hypertension (PAH)

- Idiopathic (IPAH)
- Familial (FPAH)
- Associated with (APAH):*
    - Connective tissue disorder (e.g., rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), scleroderma, systemic sclerosis (formerly known as CREST syndrome)
    - Congenital systemic-to-pulmonary shunts (e.g., congenital heart disease (CHD), including atrial or ventricular septal defect, patent ductus arteriosus (PDA), patent foramen ovale (PFO), truncus arteriosus, Eisenmenger syndrome, tetralogy of Fallot, transposition of the great vessels)
    - Portal hypertension
    - HIV infection
    - Drugs and toxins (e.g., anorexic agents, cocaine, methamphetamine, L-tryptophan)
    - Other (thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies (e.g., sickle cell anemia, thalassemia), chronic myeloproliferative disorders, splenectomy)
- Associated with significant venous or capillary involvement
    - Pulmonary veno-occlusive disease (PVOD)
    - Pulmonary capillary hemangiomatosis (PCH)
- Persistent pulmonary hypertension of the newborn

* Diagnoses, include, but are not limited to these common diagnoses.

Appendix II: Revised WHO Classification of PH – Groups 2-5 [4]

Group 2. Pulmonary hypertension with left heart disease

- Left-sided atrial or ventricular heart disease (systolic dysfunction, diastolic dysfunction)
- Left-sided valvular heart disease

Group 3. Pulmonary hypertension associated with lung diseases and/or hypoxemia

- Chronic obstructive pulmonary disease (COPD)
- Interstitial lung disease (e.g., idiopathic pulmonary fibrosis)
- Sleep disordered breathing (e.g., obstructive sleep apnea (OSA))
- Alveolar hypoventilation disorders
- Chronic exposure to high altitude
- Developmental abnormalities

Group 4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease (CTEPH)

- Thromboembolic obstruction of proximal pulmonary arteries
- Thromboembolic obstruction of distal pulmonary arteries
- Nonthrombotic pulmonary embolism (tumor, parasites, foreign material)

Group 5. Miscellaneous

- Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

Appendix III: Functional Status with Heart Failure

World Health Organization (WHO) functional class (FC) assessment classification: [49]

Class I:	Patients with pulmonary hypertension (PH) but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.
Class II:	Patients with PH resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class III:	Patients with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class IV:	Patients with PH with inability to carry out any physical activity without symptoms. These patients manifest signs of right-heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by physical activity.

New York Heart Association (NYHA) Heart Failure Classification: [50]

Class I:	Patients with no limitation of activities; they suffer no symptoms from ordinary activities.
Class II:	Patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.
Class III:	Patients with marked limitation of activity; they are comfortable only at rest.
Class IV:	Patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

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Revision History

Revision Date	Revision Summary
6/20/2024	• Added Opsynvi (macitentan and tadalafil), a newly approved combination product, to coverage criteria. • Added Winrevair (sotatercept), a newly approved subcutaneous agent, for use as an add-on to current dual or triple standard of care background PAH regimens, in those with WHO functional class II or III only. • Tyvaso DPI (treprostinil inhalation) to policy.
03/21/2024	• Updated coverage criteria/step therapy for Adempas (riociguat), Uptravi (selexipag oral), and Orenitram (treprostinil oral) to include tadalafil in criterion i and use of *either* generic ambrisentan OR generic bosentan in criterion ii.
3/16/2023	• Clarification of step therapy for branded medications with an available generic, to be consistent with COT criteria. • Added bosentan for Behçet's disease to "Investigational Uses."
3/18/2022	Effective 6/1/2022: • Clarification of Continuation of Therapy (COT) criteria, with addition of step therapy for branded medications with an available generic. • Added Uptravi IV, a newly approved formulation. Use of Uptravi IV is considered "not medically necessary" in the outpatient setting. Use in the acute (inpatient) setting is not subject to pre-authorization UM review. • Add step therapy with bosentan and ambrisentan for coverage of highest cost options (Uptravi, Orenitram, and Adempas). • Removed treprostinil injection (generic, Remodulin) from the policy (no UM).
7/16/2021	Effective 10/1/2021: • Removed sildenafil step therapy requirement from criteria for oral endothelin receptor antagonists (ERAs). • Added step therapy with generic treprostinil injection as a requirement for coverage of brand treprostinil injection (Remodulin). • Added coverage criteria for use of Tyvaso (treprostinil inhalation) in pulmonary hypertension (PH) associated with interstitial lung disease (PH-ILD), a newly FDA-approved indication.
4/22/2020	New policy (effective 7/1/2020). Replaces individual drug coverage policies for medications for PAH (dru218, dru219, dru220, dru221, dru222, dru322, dru324, dru337, dru446). No change to intent of coverage from previous: limits coverage to patients with Group 1 PAH (or CTEPH for riociguat only), step therapy with low-cost generics for oral medications for PAH (sildenafil, ambrisentan and bosentan) and use of quantity limits.

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Medication Policy Manual

Policy No: dru634

Topic: Palforzia, peanut (Arachis hypogaea) allergen oral powder-dnfp

Date of Origin: May 15, 2020

Committee Approval Date: March 21, 2024

Next Review Date: 2025

Effective Date: June 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Peanut (Arachis hypogaea) allergen oral powder-dnfp (Palforzia) is a medication used for people with severe peanut allergy to reduce the risk of allergic reactions due to accidental exposure to peanut.

Policy/Criteria

I. Continuation of therapy (COT): Palforzia may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Palforzia may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A through C are met.

A. Palforzia is prescribed by an allergist or immunologist.

AND

B. The member has a **confirmed diagnosis of peanut allergy** based on one of the following:

1. A positive peanut specific immunoglobulin E (IgE) test for peanut allergy.

OR

2. A positive skin prick test (SPT) to peanut protein.

OR

3. Oral food challenge.

AND

C. The patient is age 4 to 17 years at the time of initiating treatment with Palforzia.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Palforzia coverable under the pharmacy benefit (as a self-administered medication) OR coverable under the medical benefit (as a provider-administered medication) depending on dose phase.

B. When pre-authorization is approved, Palforzia will be authorized in a quantity sufficient for up to a 30-day supply.

C. Authorization may be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) may be required to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement including reduction in the frequency and severity of peanut allergy reactions as compared to prior to starting.

Position Statement

Summary

- The intent of this policy is to limit coverage of Palforzia for the indication and dose for which it has been shown to be safe and effective in clinical trials (i.e., patients age 4 to 17 years with a confirmed diagnosis of peanut allergy as specified in the coverage criteria above).
- Palforzia is FDA approved to for the mitigation of allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut. [1]
- Clinical trials of Palforzia showed an increase in the percentage of patients who could ingest peanut protein during a food challenge (600 mg of peanut protein). [2] The clinical meaningfulness of the ability to tolerate 600 mg of peanut protein is uncertain, and it is unclear if treatment provides benefit over strict avoidance of peanuts alone. In addition, there was an increase in systemic allergic reactions and the need for epinephrine, such that the risk versus benefit must be carefully considered.
- In clinical trials for Palforzia, the diagnosis of peanut allergy was confirmed through skin prick testing or serum peanut specific IgE levels. [2] Oral food challenges may also be used to confirm the diagnosis. [3]
- Palforzia has a complex dosing regimen which requires strict adherence. Dose initiation and dose increases must be done under the supervision of a healthcare provider. [1]
- Palforzia has several serious warnings related to its use, including: anaphylaxis (can occur at any time during therapy), not for use in patients with uncontrolled, severe, or steroid-dependent asthma, risk of eosinophilic esophagitis, and GI adverse events. [1 4]

- There is limited data on long-term durability and safety for Palforzia. Initial Palforzia trials were limited to 20 to 40 weeks of up-dosing followed by 24 to 28 weeks of maintenance dosing. A two-year open-label follow-on study found that daily dosing regimens were better tolerated than nondaily regimens. [5] However, it is currently unknown if Palforzia maintains safety and efficacy if patients are not consistently adherent. If patients do not continuously adhere to treatment, including the specifics of the dose titration, they may become allergic to the treatment itself and have a reaction if they restart. [1 6]
- The use of Palforzia for any other condition or type of allergy is considered investigational. In addition, the use of more than one peanut allergy treatment at a time is considered investigational.

Clinical Efficacy - Palforzia

- Palforzia was evaluated in one phase 3, double-blind, randomized, placebo-controlled trial (PALISADE) for desensitization and improvement in ability to ingest peanut protein during a food challenge. [2]
    * The study included patients ages 4 to 55 years with confirmed peanut allergy. However, efficacy was only evaluated in patients from 4 to 17 years of age. There is no safety or efficacy data in patients less than 4 years of age.
    * The primary endpoint was desensitization in patients ages 4 to 17 after 24 to 28 weeks of maintenance therapy.
    * Desensitization was defined as the proportion of subjects able to ingest 600 mg or more of peanut protein during a double-blind, placebo-controlled, food challenge (DBPCFC).
    * 67% of patients who received Palforzia were able to tolerate 600 mg of peanut protein compared to 4% of patients who received placebo.
    * The ability to tolerate 600 mg of peanut protein is of uncertain clinical relevance. There is no consensus on what tolerated dose is considered clinically relevant. [6]
    * Endpoints such as a decrease in reactions to accidental exposure to peanuts, need for emergency medical treatment (such as epinephrine use, emergency department visits, or hospitalization), quality of life, or other patient centric outcomes would be more meaningful.
- Patients were randomized to receive Palforzia or placebo. Doses of Palforzia were escalated to 300 mg daily with an increase every two weeks within a 40-week period. All dose-escalations took place in-office. Maintenance therapy of 300 mg daily was then continued for 24 weeks. At the end of 24 weeks of maintenance therapy, patients completed a DBPCFC to assess the primary endpoint.
- Although a significantly higher percentage of patients were able to tolerate 600 mg of peanut protein, the rate of systemic allergic reactions and use of epinephrine was higher in patients who received Palforzia.

PALISADE Study	Palforzia (n = 372)	Placebo (n = 124)	P-value
Proportion of Subjects Able to Ingest 600 mg of peanut protein or more, without dose-limiting symptoms (n, %)	250 (67.2%)	5 (4.0%)	P<0.001
Systemic allergic reactions	14.2%	3.2%	N/A
Use of epinephrine outside of the DBPCFC	14.0.%	6.5%	N/A

Investigational Uses:

- At this time, Palforzia has not been studied for any indication other than peanut allergy. Therefore, the use of Palforzia for any other condition or type of allergy is considered investigational.

Dosing [1]

- Palforzia is given in three phases (see Prescribing Information for full details). The first two phases are complex and require strict adherence. The maintenance dose is 300 mg per day.
    * Initial dosing and each dose increase during the up-dosing phase must be administered by a healthcare professional in a certified setting. Patients must be monitored for at least 60 minutes to following each provider-administered dose.
    * Preparation: The Palforzia capsules or sachets are opened, and the enclosed powder is mixed into semisolid food prior to consuming by mouth immediately.
    * Initial Dose Escalation: Single doses of 0.5 mg up to 6 mg are administered at 20- to 30-minute intervals on day 1. On day 2, tolerability for 3 mg is confirmed and the patient moves into the up-dosing phase.
    * Up-Dosing: The dose is gradually increased from 3 mg to 300 mg with dose increases every two weeks.
    * Maintenance: 300 mg daily
    * For up-dosing, if the patient tolerates the first dose of the increased dose level, the patient may continue that dose level at home.

Safety [1]

- Due to safety concerns, Palforzia is only available through a restricted program called the PALFORZIA REMS. The program requires that providers, pharmacies, and healthcare settings are certified prior to use of Palforzia. Patients must also be enrolled in the REMS program. The program is designed to ensure that all stakeholders are aware of the risks and benefits of Palforzia, the signs of anaphylaxis, monitoring requirements, and that patients have access to injectable epinephrine at all times. [1 4]
- Palforzia has several serious warnings related to its use, including:
    * Palforzia oral can cause anaphylaxis that can occur at any time during therapy.
    * Palforzia oral should not be started in patients with uncontrolled asthma. It is a risk factor for worse outcomes with any anaphylactic reaction. Additionally, Palforzia oral has not been studied in patients with severe asthma, persistently uncontrolled asthma, or patients on long-term systemic corticosteroid therapy.

* Palforzia oral is associated with eosinophilic esophagitis, a serious form of inflammation in the esophagus.
* Palforzia oral is associated with high rates of mild to moderate gastrointestinal adverse reactions, such as abdominal pain, vomiting, nausea, oral pruritus, and oral paresthesia, which may impact tolerability.

- Palforzia has an unclear long-term risk-benefit profile due to the risk of serious allergic reactions and anaphylaxis and limited evidence for improvements in quality of life or reductions in systemic allergic reactions compared to strict avoidance of peanuts alone. Additional long-term studies will be needed to determine impacts on these endpoints and further assess the long-term safety profile.

Appendix 1: Palforzia: Commercial Packaging for Self-Administration		
Packaging	**Kit Components (Capsules or Sachets)**	**Number of Doses per Kit**
Initial Dosing Escalation	Each pack contains 13 capsules: ▪ 0.5 mg (Level A) One 0.5 mg capsule ▪ 1 mg (Level B) One 1 mg capsule ▪ 1.5 mg (Level C) One 0.5 mg capsule; One 1 mg capsule ▪ 3 mg (Level D) Three 1 mg capsules ▪ 6 mg (Level E) Six 1 mg capsules	5
Up-Dosing		
3 mg (Level 1)	Forty-five 1 mg capsules	15
6 mg (Level 2)	Ninety 1 mg capsules	15
12 mg (Level 3)	Thirty 1 mg capsules; Fifteen 10 mg capsules	15
20 mg (Level 4)	Fifteen 20 mg capsules	15
40 mg (Level 5)	Thirty 20 mg capsules	15
80 mg (Level 6)	Sixty 20 mg capsules	15
120 mg (Level 7)	Fifteen 20 mg capsules; Fifteen 100 mg capsules	15
160 mg (Level 8)	Forty-five 20 mg capsules; Fifteen 100 mg capsules	15
200 mg (Level 9)	Thirty 100 mg capsules	15
240 mg (Level 10)	Thirty 20 mg capsules; Thirty 100 mg capsules	15
300 mg (Level 11)	Fifteen 300 mg sachets	15
Maintenance		
300 mg (Level 11)	Thirty 300 mg sachets	30

Cross References
BlueCross BlueShield Association Medical Policy, 5.01.36 - Desensitization Treatment for Peanut Allergies. [July 2023]
Sublingual Immunotherapy as a Technique of Allergen Specific Therapy, Medical Policy Manual, Policy No. 121

References

1. Palforzia [Prescribing Information]. Brisbane, CA: Aimmune Therapeutics, Inc; January 2020
2. Vickery BP, Vereda A, Casale TB, et al. AR101 Oral Immunotherapy for Peanut Allergy. *The New England journal of medicine.* 2018;379(21):1991-2001. PMID: 30449234
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4. PALFORZIA REMS Program. Secondary PALFORZIA REMS Program [cited 2/26/2020]. 'Available from:' www.palforziarems.com.
5. Vickery BP, Vereda A, Nilsson C, et al. Continuous and Daily Oral Immunotherapy for Peanut Allergy: Results from a 2-Year Open-Label Follow-On Study. *J Allergy Clin Immunol Pract.* 2021;9(5):1879-89 e14. PMID: 33359589
6. Institute for Clinical and Economic Review, Oral Immunotherapy and Viaskin® Peanut for Peanut Allergy: Effectiveness and Value: https://icer-review.org/topic/peanut-allergy/. Accessed: 12/1/2019

Revision History

Revision Date	Revision Summary
3/21/2024	No criteria changes with this annual review.
3/16/2023	No criteria changes made with this annual update.
6/17/2022	No criteria changes made with this annual update.
4/21/2021	• Added oral food challenge as a diagnostic option to confirm the diagnosis of peanut allergy. • Update 'Investigational Uses' - removed 'use with Viaskin' (not FDA approved)
7/22/2020	Revised diagnostic criteria to require a positive peanut specific IgE test or skin prick test.
6/1/2020	Correction to lab values.
4/22/2020	New policy (effective 5/15/2020). Limits coverage to patients with a confirmed diagnosis of peanut allergy the setting in which it was studied and has a labeled indication.

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Medication Policy Manual	**Policy No:** dru637
Topic: Jelmyto, mitomycin for pyelocalyceal solution (mitomycin hydrogel)	**Date of Origin:** August 15, 2020
Committee Approval Date: December 7, 2023	**Next Review Date:** 2024
Effective Date: March 1, 2024	

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Jelmyto (mitomycin hydrogel for pyelocalyceal use) is chemotherapy medication used for specific types of cancer [low-grade Upper Tract Urothelial Cancer (LG-UTUC)]. It is a new formulation of mitomycin that is given directly into the urinary tract (ureters). It is administered by a trained provider via a catheter (ureteral catheter or nephrostomy tube). It is **not** for intravenous (IV) use.

PLEASE NOTE: This policy and the coverage criteria below do not apply to mitomycin injection (generic Mitomycin-C). Generic mitomycin injection (Mitomycin-C) does not require pre-authorization.

Policy/Criteria

Most contracts require pre-authorization approval of Jelmyto (mitomycin hydrogel for pyelocalyceal use) prior to coverage.

I. Continuation of therapy (COT): Jelmyto (mitomycin hydrogel for pyelocalyceal use) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Jelmyto (mitomycin hydrogel for pyelocalyceal use) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that the patient has a diagnosis of **low-grade Upper Tract Urothelial Carcinoma (LG-UTUC)**.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Jelmyto (mitomycin hydrogel for pyelocalyceal use) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, up to 17 Jelmyto (mitomycin hydrogel for pyelocalyceal use) single-dose cartons (2x 40-mg vials) may be authorized per treatment course (up to 14 months).

IV. Jelmyto (mitomycin hydrogel for pyelocalyceal use) is considered investigational when used for all other conditions, including use for intravenous (IV) infusion.

Position Statement

Summary

- Jelmyto (mitomycin hydrogel for pyelocalyceal use) is a new formulation of mitomycin that is instilled into the ureters via a ureteral catheter or nephrostomy tube in patients with low-grade Upper Tract Urothelial Carcinoma (LG-UTUC). It is administered in a provider's office.
- The intent of this policy is to allow coverage of Jelmyto (mitomycin hydrogel for pyelocalyceal use) where it has been evaluated and shown to be effective, up to the dose shown to be safe and effective in clinical trials.
- The evidence for Jelmyto (mitomycin hydrogel for pyelocalyceal use) is based on a small, non-comparative, non-blinded trial that evaluated tumor response rates in patients with LG-UTUC (low quality evidence). Although this therapy appears promising based on the disappearance of tumors in a fair proportion of patients, additional study is needed to better define its clinical benefit (e.g., preserve kidneys, improve overall survival).
- The National Comprehensive Cancer Network (NCCN) urothelial carcinoma guideline recommends using Jelmyto (mitomycin hydrogel for pyelocalyceal use) for LG-UTUC after complete or near complete endoscopic resection or ablation for low-volume (5 mm to 15 mm) residual tumors.
- Jelmyto (mitomycin hydrogel for pyelocalyceal use) is instilled weekly for six weeks in the providers office. Patients with a complete response three months after therapy is initiated may receive up to 11 additional monthly maintenance doses.
- The maximum dose of Jelmyto (mitomycin hydrogel for pyelocalyceal use) is 15 ml (60 mg of mitomycin) per instillation. Each single-dose carton contains two 40 mg vials.
- There is insufficient evidence to support the use of Jelmyto (mitomycin hydrogel for pyelocalyceal use) for any other indication.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.

- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy

- The evidence for Jelmyto (mitomycin hydrogel for pyelocalyceal use) is based on a small, non-comparative, non-blinded trial [OLYMPUS] that evaluated complete tumor response at 3 months in adult patients with LG-UTUC. [1,2]
    * Patients had either newly diagnosed or recurrent disease, and had at least one papillary low-grade tumor measuring at least 5 mm but no larger than 15 mm.
    * A complete response (tumor disappearance) was seen in 58% of patients at 3 months. Forty-six percent of patients had an ongoing complete response at the 12-month visit.
- Tumor response is a surrogate endpoint. Although the high number of complete responses is promising, additional study is needed to evaluate meaningful clinical outcomes such as preservation of kidneys, or improved overall survival or quality of life.
- The National Comprehensive Cancer Network (NCCN) urothelial carcinoma guideline recommends using Jelmyto (mitomycin hydrogel for pyelocalyceal use) for LG-UTUC after complete or near complete endoscopic resection or ablation for low-volume (5 mm to 15 mm) residual tumors (category 2A recommendation). [3]

Investigational Uses

- The safety and efficacy of Jelmyto (mitomycin hydrogel for pyelocalyceal use) have only been evaluated in adult patients with LG-UTUC.
- There are no other accepted therapeutic uses for this new mitomycin formulation.

Safety [1]

- Grade 3 or greater adverse events (AEs) that occurred in at least 2% of subjects in the pivotal Jelmyto (mitomycin hydrogel for pyelocalyceal use) clinical trial included ureteric stenosis, hydronephrosis, flank pain, urinary tract infection, hematuria, renal dysfunction, and vomiting.
- About one-quarter of patients enrolled in the pivotal trial discontinued Jelmyto (mitomycin hydrogel for pyelocalyceal use) due to a side effect.

Dosing [1]

- Each Jelmyto (mitomycin hydrogel for pyelocalyceal use) kit (containing two 40-mg single-dose vials of and one vial of sterile hydrogel for reconstitution) is suitable for one instillation.
- Jelmyto (mitomycin hydrogel for pyelocalyceal use) must be administered by a trained provider.
- The actual dose of Jelmyto (mitomycin hydrogel for pyelocalyceal use) is determined based on volumetric measurements using pyelography. The maximum dose per instillation is 15 ml (60 mg mitomycin).
- Dosing schedule:
    * ***Initial dose:*** one instillation weekly for six weeks.

* ***Maintenance:*** If a complete response is maintained three months from the initiation of therapy, up to 11 additional monthly instillations of Jelmyto (mitomycin hydrogel for pyelocalyceal use) may be given.
* The safety and efficacy of Jelmyto (mitomycin hydrogel for pyelocalyceal use) beyond 17 total instillations (one treatment course) has not been studied.

Codes	Number	Description
HCPCS	J9281	Mitomycin pyelocalyceal instillation (Jelmyto), 1 mg

References

1. Jelmyto® (mitomycin for pyelocalyceal solution) [package insert]. UroGen Pharma, Inc.; Princeton, NJ; September 2022.
2. Kleinmann N, Matin SF, Pierorazio PM, et al. Primary chemoablation of low-grade upper tract urothelial carcinoma using UGN-101, a mitomycin-containing reverse thermal gel (OLYMPUS): an open-label, single-arm, phase 3 trial. *Lancet Oncol.* 2020;21(6):776-85. PMID: 32631491
3. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology™. [Updated routinely]. [cited with policy updates and as necessary]. Available from: https://www.nccn.org/guidelines/category_1.

Revision History

Revision Date	Revision Summary
12/7/2023	No criteria changes with this annual review.
12/9/2022	• Updated standard language in policy. • No changes to coverage criteria with this annual update.
1/20/2021	• Updated continuation of therapy (COT) language. • No changes to coverage criteria.
7/22/2020	New policy (effective 8/15/2020). Limits coverage to adult patients with LG-UTUC for up to 17 total instillations (one single-dose carton includes 2 x 40 mg vials of mitomycin for pyelocalyceal use).

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Medication Policy Manual

Policy No: dru640

Topic: Viltepso, viltolarsen

Date of Origin: June 15, 2020

Committee Approval Date: June 20, 2024

Next Review Date: 2024

Effective Date October 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Viltepso (viltolarsen) is an intravenous medication that may be used for Duchenne muscular dystrophy (DMD) when patients have a specific gene mutation. A clinical benefit, such as improved ambulation, of Viltepso (viltolarsen) has not been established.

Policy/Criteria

Most contracts require pre-authorization approval of Viltepso (viltolarsen) prior to coverage.

I. Continuation of therapy (COT): Viltepso (viltolarsen) is considered investigational for all conditions, per the full policy criteria below.

Please note: *Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Viltepso (viltolarsen) is considered investigational for all conditions, including Duchenne muscular dystrophy (DMD) that is amenable to exon 53 skipping (Table 1). However, if found to be medically necessary, criteria A must also be met:

A. Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, Site of Care Review, dru408].

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Viltepso (viltolarsen) coverable under the medical benefit (as a provider administered medication).

B. Although the use of Viltepso (viltolarsen) is considered investigational for all conditions, including DMD that is amenable to exon 53 skipping, if pre-authorization is approved, Viltepso (viltolarsen) will be authorized in doses up to 80 mg/kg every week. (52 infusions per year).

C. Authorization shall be reviewed at least every twelve months for documented benefit. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met. Specifically, documentation that the medication is providing clinical benefit, including disease stability or improvement, and lack of disease progression.

Position Statement

Summary

- Viltepso (viltolarsen) is an intravenous therapy indicated for the treatment of Duchenne muscular dystrophy (DMD) when there is a confirmed mutation of the DMD gene that is amenable to exon 53 skipping. It was approved through the FDA Accelerated Approval Program based on an increase in dystrophin in skeletal muscles observed in some patients during a phase II trial. [1]
- A clinical benefit (e.g. prolongation of independent ambulation, improved quality of life, or prevention of disease progression and disability) of Viltepso (viltolarsen) has not been established.
  * In one open-label trial in a total of 16 patients, of which only 8 received the approved dose, Viltepso (viltolarsen) was shown to increase dystrophin levels. However, it has not been proven that an increase in dystrophin will translate to improved clinical outcomes, such as improved motor function.

- The U.S. Centers for Disease Control and Prevention (CDC) has developed general management guidelines for DMD. The CDC recommends corticosteroids and supportive care to slow disease progression. These guidelines were published prior to the submission of Viltepso (viltolarsen) to the FDA, thus the use of Viltepso (viltolarsen) for DMD has not yet been addressed. [2-4]

Clinical Efficacy[5]

- Evidence regarding the effect of Viltepso (viltolarsen) on dystrophin levels is inconclusive. Data is limited to a small, two-part, dose escalation, phase II trial. Additional, larger, well-controlled trials are needed to establish the safety and efficacy of Viltepso (viltolarsen) in Duchenne muscular dystrophy (DMD).
- In the phase II trial, 16 patients were initially randomized to receive either placebo (n=5), Viltepso (viltolarsen) 40 mg/kg (n=6), or Viltepso (viltolarsen) 80 mg/kg (n=5) via intravenous route weekly for 4 weeks. After 4 weeks, all patients, received open-label Viltepso (viltolarsen) at a dose of either 40 mg/kg (n=8) or 80 mg/kg (n=8) intravenously once weekly. The mean dystrophin levels increased to 5.9% of normal in the Viltepso (viltolarsen) 80 mg/kg group; the approved dose, at 25 weeks.
    * Dystrophin production is a surrogate biomarker of disease improvement with an unknown correlation to health outcomes.
    * An absolute increase in dystrophin levels has not been correlated to improved ambulation or muscle function and a minimal clinically important difference in dystrophin levels has not yet been established. Experts have proposed that dystrophin levels greater than or equal to 10% of normal may be clinically meaningful; however, validation is needed
- Lack of an appropriate control group, duration, and size of the Viltepso (viltolarsen) trial, makes it impossible to demonstrate any meaningful conclusions regarding endpoints with functional outcomes, including 6MWT and pulmonary function resulting from Viltepso (viltolarsen) treatment. Long-term comparative evidence is needed to further clarify the role of Viltepso (viltolarsen).[6]
- Viltepso (viltolarsen) has not yet been shown to improve any clinical outcomes such as quality of life, prolongation of independent ambulation, or prevention of disease progression and disability.

Safety [1]

- Limited safety data is available, however, the most common adverse reactions reported with Viltepso (viltolarsen) during trials included upper respiratory tract infections, injection site reactions, cough, and pyrexia.
- Viltepso (viltolarsen) contains a warning for kidney toxicity based on experience with other antisense oligonucleotides. Monitoring of kidney function is recommended.

Table 1: Mutations Amenable to Exon 53 skipping			
19-52	29-52	37-52	47-52
21-52	30-52	38-52	48-52
23-52	31-52	39-52	49-52
24-52	32-52	40-52	50-52
25-52	33-52	41-52	52
26-52	34-52	42-52	54-58
27-52	35-52	43-52	54-61
28-52	36-52	45-52	54-63

Cross References
BlueCross BlueShield Association Medical Policy, 5.01.27 - Treatment for Duchenne Muscular Dystrophy [June 2023]
BlueCross BlueShield Association Medical Policy, Gene Therapies for Duchenne Muscular Dystrophy [October 2023]
Exondys 51, eteplirsen, Medication Policy Manual, Policy No. dru480
Vyondys 53, golodirsen, Medication Policy Manual, Policy No. dru606
Amondys 45, casimersen, Medication Policy Manual, Policy No. dru661
Elevidys, delandistrogene moxeparvovec, Medication Policy Manual, Policy No. dru754
Site of Care Review, Medication Policy Manual, Policy No. dru408

Codes	Number	Description
HCPCS	J1427	Injection, viltolarsen (Viltepso), 10 mg
ICD-10	G71.0	Muscular dystrophy

References

1. Viltepso [Prescribing Information]. Paramus, NJ: NS Pharma; March 2021
2. Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. *The Lancet Neurology*. 2018;17(3):251-67. PMID: 29395989
3. Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management. *The Lancet Neurology*. 2018;17(4):347-61. PMID: 29395990
4. Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 3: primary care, emergency management, psychosocial care, and transitions of care across the lifespan. *The Lancet Neurology*. 2018;17(5):445-55. PMID: 29398641
5. Clemens PR, Rao VK, Connolly AM, et al. Safety, Tolerability, and Efficacy of Viltolarsen in Boys With Duchenne Muscular Dystrophy Amenable to Exon 53 Skipping: A Phase 2 Randomized Clinical Trial. JAMA Neurol. United States, 2020.
6. Clemens PR, Rao VK, Connolly AM, et al. Long-Term Functional Efficacy and Safety of Viltolarsen in Patients with Duchenne Muscular Dystrophy. J Neuromuscul Dis. Netherlands, 2022:493-501.

Revision History

Revision Date	Revision Summary
6/20/2024	Added Viltepso to site of care (SOC) program (effective 10/1/2024).
12/7/2023	• Added quantity limit and reauthorization criteria (no change to intent) • Updated cross references.
12/9/2022	No criteria changes with this annual update.
1/20/2021	No criteria changes with this annual update.
10/28/2020	Updated policy name and position statement based on FDA approved prescribing information. No change to intent of policy.
6/15/2020	New policy. Effective 6/15/2020. Use of viltolarsen is considered investigational in the treatment of all conditions, including Duchenne muscular dystrophy (DMD) that is amenable to exon 53 skipping. The available clinical trial data was insufficient to demonstrate safety or efficacy of viltolarsen in the treatment of DMD.

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Medication Policy Manual | **Policy No:** dru641

Topic: Roctavian, valoctocogene roxaparvovec | **Date of Origin:** August 15, 2020

Committee Approval Date: June 20, 2024 | **Next Review Date:** 2025

Effective Date: July 15, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Valoctocogene roxaparvovec (Roctavian) is a gene therapy for the treatment of adults with severe hemophilia A, a rare hematologic condition that results in impaired clotting and bleeding episodes. It is given as a single, one-time intravenous (IV) infusion.

Policy/Criteria

I. Roctavian (valoctocogene roxaparvovec) is considered investigational, except for those situations specifically addressed in the policy criteria below.

PLEASE NOTE: Under this criterion, any gene therapy products for hemophilia B not specifically addressed in this policy will be considered investigational.

II. Continuation of therapy (COT): Roctavian (valoctocogene roxaparvovec) may be considered medically necessary when full policy criteria below are met, including quantity limit. However, Roctavian (valoctocogene roxaparvovec) is not coverable for repeated doses and is not coverable if a patient has previously received prior Roctavian (valoctocogene roxaparvovec) or any other gene therapy products for hemophilia A.

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

III. New starts (treatment-naïve patients): The use of Roctavian (valoctocogene roxaparvovec) is considered not medically necessary for the treatment of patients with severe hemophilia A.

IV. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Roctavian (valoctocogene roxaparvovec) coverable only under the medical benefit (as a provider-administered medication).

B. Although the use of Roctavian (valoctocogene roxaparvovec) for hemophilia A is considered not medically necessary. If pre-authorization is approved, Roctavian (valoctocogene roxaparvovec) may be authorized in a quantity up to 6×10^{13} vg/kg given intravenously once, for one treatment course per lifetime.

C. Additional infusions of Roctavian (valoctocogene roxaparvovec) will not be authorized.

V. Investigational Uses

A. Repeated doses of Roctavian (valoctocogene roxaparvovec) or any other gene therapy products for hemophilia A, including Roctavian (valoctocogene roxaparvovec) previously given as part of a clinical trial.

B. Combination use with Hemlibra (emicizumab).

C. Use in all other conditions not otherwise specified in the coverage criteria above.

Position Statement

Summary

- Hemophilia A (SMA) is a rare X-linked congenital bleeding disorder caused by a deficiency of coagulation FVIII, part of the intrinsic coagulation pathway. A deficiency in circulating FVIII leads to impaired clotting and bleeding episodes.
- Severe hemophilia A is characterized by a FVIII level of less than 1 IU/dL and spontaneous bleeding into the joints and muscles. Symptoms often begin in early infancy.
- Roctavian (valoctocogene roxaparvovec) is an adeno-associated virus (AAV) vector-based gene therapy which replaces the defective FVIII gene.
- Safety and efficacy data comes from what has been reported in two ongoing clinical trials of Roctavian (valoctocogene roxaparvovec). This includes a small phase 1/2, single-arm safety trial, of which only seven patients received the proposed therapeutic dose, and the pivotal non-comparative phase 3 trial.
    * All enrolled patients were >18 years of age, with severe hemophilia A (baseline FVIII level ≤ 1 IU/dL) and no history of inhibitors to FVIII or antibodies to the viral vector (AAV5).
    * Patients were followed for a period of 3 years after the Roctavian (valoctocogene roxaparvovec) infusion in both trials.
    * In the pivotal phase 3 GENEr8-1 trial, Roctavian (valoctocogene roxaparvovec) reported non-inferiority based on a 2.8 average annual bleed rate (ABR) reduction for all bleeds (2.6 vs 5.4), when compared to a 6-month run in phase of exogenous FVIII therapy.[1]
- Treatment of hemophilia A is highly individualized and differs by region and provider preference. Existing treatment options, including Hemlibra (emicizumab) and exogenous FVIII therapies, have a high clinical burden due to life-long use. However, they are very effective in reducing bleeds and improving quality of life (QOL) in patients with hemophilia and are guidelines recommended standard of care therapy. Furthermore, exogenous FVIII products have decades of clinical data backing up their safety and efficacy in this population. [2]
- Currently available data has not established that Roctavian (valoctocogene roxaparvovec) improves clinically meaningful endpoints such as bleeding rates or joint complications compared to standard of care.
    * There is no comparative data.
    * The published phase 3 trial did not optimize prophylaxis with exogenous factor products during the run-in period.
    * A significant difference between reported median and mean bleeding rate suggests a highly heterogenous degree of control during the run-in period.
    * Due to differing standards of care across trial sites, there is insufficient data to draw conclusions regarding the comparative effectiveness of Roctavian (valoctocogene roxaparvovec) versus prophylaxis with exogenous factor or Hemlibra (emicizumab).

- Observed bleeding rates in clinical trials and low overall factor usage in the trial population have established that Roctavian (valoctocogene roxaparvovec) is effective in controlling bleeding in patients with Hemophilia A; however, long-term safety and durability of response have yet to be established.
- Trial subjects were eligible only if they received prophylaxis with exogenous factor VIII; there is no data on crossover from Hemlibra (emicizumab). Phase III data has also shown that FVIII expression will decrease over time. The timing, safety, and best practice standards for the inevitable transition back to regular prophylaxis with infused exogenous factor VIII or Hemlibra (emicizumab) has yet to be established.
- Given the current costs, the unclear safety record, the uncertain durability of response, and the availability of standard of care FVIII replacement therapies the use of Roctavian (valoctocogene roxaparvovec) in hemophilia A is considered not medically necessary.

Clinical Efficacy

Severe Hemophilia A[1, 3-5]

Roctavian (valoctocogene roxaparvovec) was FDA approved based on the results of two open-label trials in patients with severe hemophilia A (baseline FVIII level <1 IU/dL). Patients in both trials were greater than 18 years of age and did not have a history FVIII inhibitors, antibodies to AAV5, or any existing liver abnormalities.

- The first trial is an ongoing phase 1/2 dose-finding and safety trial. Although the trial enrolled a total of 15 patients, only seven received the proposed therapeutic dose ($6x10^{13}$ vg/kg). Patients were to be followed for five years.
    * The primary endpoints were the number of treatment-related adverse events and a dose determination of valoctocogene roxaparvovec required to achieve expression of FVIII at or above 5% of normal activity (≥5 IU/dL).
    * Secondary endpoints with clinical relevance included annualized bleeding events and frequency of exogenous FVIII replacement. These endpoints are available out to three years post infusion in the therapeutic cohort (n=7).
        - A significant reduction in mean FVIII expression was seen between year 1 and 2 (64 IU/dL vs 36 IU/dL), followed by a smaller reduction between year 2 and 3 (36IU/dL vs 33 IU/dL).
        - The mean annualized bleeding rate (ABR) decreased to 0.7±1.6, a significant decrease from the baseline of 16.3 ±15.7.
- The second pivotal trial, GENEr8-1 (N=134), is an unpublished ongoing multicenter, single arm (non-comparative), phase 3, non-inferiority trial in which all subjects receive a single infusion of Roctavian (valoctocogene roxaparvovec) at a dose of $6x10^{13}$ vg/kg.
    * The primary endpoint for this trial was the change from baseline in ABR for all bleeds during the efficacy evaluation period (EEP), which ranged from 1.7 to 3.7 years post-infusion at the last data analysis.
    * Clinically relevant secondary endpoints included the change in the annualized utilization of exogenous FVIII replacement therapy and the annualized number of bleeding episodes requiring exogenous FVIII replacement treatment during the EEP.

    * At the EEP, non-inferiority was achieved as the reported average ABR was 2.6 for all bleeds, which was a reduction from the average ABR of 5.4 that was reported during the 6-month run in on FVIII treatment.
    * At the year 3 data analysis, only 10.6% of subjects had factor VIII activity > 40 IU/dL. 24.2%, and 56.1% of subjects had factor VIII activity consistent with moderate-severe and mild hemophilia, respectively.
    * The available trial data and modelling suggest that bleeding risk will rise at factor VIII activity of approximately 5 IU/dL; 33.3% of study subjects were observed to have factor levels < 5 IU/dL at year 3. Models developed from trial data suggest that median factor VIII activity will decline to 5.7 IU/dL by week 260.
    * Seventeen subjects (12.6%) resumed prophylactic therapy across the entire trial population (N=134) at 3 years post treatment.
- This trial had the following significant limitations which impact the confidence in the data:
    * Lack of control comparison: There was no placebo arm in the trial; it relied on using the historical bleeding rate and factor utilization in a small number of patients. Treatment for hemophilia A is highly individualized, and the data does not allow for an assessment of the magnitude of benefit compared to therapies with proven efficacy in this population. Comparison of an active therapy to a historical control can overestimate the benefit seen with Roctavian (valoctocogene roxaparvovec).
    * Uncertainty of duration of response: The durability of treatment effect is unknown. While models have been developed based on data up to 3 years, the durability of response past that is not known.[4]
- To date, no subjects developed inhibitors to FVIII during the clinical trials.
- Subjects in the phase 3 GENEr8-1 trial had a lower FVIII response than was seen during the phase I/II trial. Outside of unexplained patient variability, it was hypothesized that this was partly attributed to differences in steroid regimens used in each trial.
    * Patients in the phase 1/2 trial began steroids earlier post-infusion (week 3 vs. week 10.9) to manage ALT elevations than in the phase 3 GENEr8-1 trial.
    * ALT elevations were associated with decreased FVIII activity in a greater percentage of patients in the phase 3 GENEr8-1 trial.

Investigational Uses

- Use in pediatrics, patients with inhibitors, or liver dysfunction: There are no proposed or ongoing trials that will look at the safety or efficacy of Roctavian (valoctocogene roxaparvovec) in patients less than 18, with inhibitors to FVIII, liver dysfunction, or with antibodies to the viral vector.
- Repeated doses: There is no evidence to establish the safety or efficacy of repeat doses of Roctavian (valoctocogene roxaparvovec). Anti-AAV5 antibodies were observed in 100% of treated subjects in clinical trials. If medical necessity criteria are met, only a single dose of Roctavian will be covered per lifetime.

Safety [1 5]

- A majority (96%) of trial subjects experienced elevated ALT levels which required treatment with immunosuppressants such as glucocorticoids. The median duration of glucocorticoid use was 35 weeks. The safety of Roctavian (valoctocogene roxaparvovec) in patients with pre-existing liver dysfunction or disease has not been established.
- No new cancers have been observed to date. There is insufficient data to assess any potential increased risk of cancers, including liver cancers.
- Although some subjects achieved supra-physiologic levels of factor VIII activity, no thromboembolic adverse events were observed.
- The most common side effects (>20% incidence) experienced during the clinical trials include ALT/AST elevations, arthralgia, nasopharyngitis, headache, back pain, fatigue, upper respiratory tract infection, arthropathy, cough, insomnia, oropharyngeal pain, diarrhea, extremity pain, acne, elevated lactate dehydrogenase, nausea, and rhinitis.
- Due to the small number of patients treated with Roctavian (valoctocogene roxaparvovec) during clinical trials, additional data is necessary to further define the safety profile.

References

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Revision History

Revision Date	Revision Summary
6/20/2024	Updated COT and quantity limit. No changes to policy intent.
7/22/2020	New policy (Effective 8/15/2020). Coverage of Roctavian (valoctocogene roxaparvovec) is considered not medically necessary for the treatment of adult hemophilia A.

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Medication Policy Manual

Policy No: dru645

Topic: Trodelvy, sacituzumab govitecan-hziy

Date of Origin: August 15, 2020

Committee Approval Date: March 6, 2025

Next Review Date: 2025

Effective Date: May 1, 2025

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Trodelvy (sacituzumab govitecan-hziy) is an intravenous medication that is used in the treatment of specific types of cancer.

Policy/Criteria

Most contracts require pre-authorization approval of Trodelvy (sacituzumab govitecan-hziy) prior to coverage.

I. Continuation of therapy (COT): Trodelvy (sacituzumab govitecan-hziy) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Trodelvy (sacituzumab govitecan-hziy) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criterion A or B below is met.

A. A diagnosis of **HER-2 negative breast cancer, advanced (locally advanced or metastatic)** when criteria 1, 2, and 3 below are met:

1. Use in one of the following settings (a or b):

a. **Triple-negative breast cancer** (TNBC)

OR

b. **Hormone receptor positive (HR+), HER-2 negative** [IHC 0, IHC 1+, or IHC2+/ISH-]

[IHC = immunohistochemistry; ISH = in situ hybridization]

AND

2. There has been disease progression on, or after, all of the following:

a. At least <u>two</u> prior lines of cytotoxic chemotherapy, at least one of which was used in the advanced setting (locally advanced or metastatic) (see *Appendix 1*).

AND

b. **<u>For HR+ only</u>**, both of the following (i and ii):

i. Prior anticancer endocrine therapy (see *Appendix 2*).

AND

ii. A CDK4/6 inhibitor (see *Appendix 3*).

AND

3. Trodelvy (sacituzumab govitecan-hziy) is used as monotherapy.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Trodelvy (sacituzumab govitecan-hziy) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Trodelvy (sacituzumab govitecan-hziy) will be authorized in quantities of up to two doses of 10 mg/kg every 21 days until disease progression.

C. Authorization **may** be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

IV. Trodelvy (sacituzumab govitecan-hziy) is considered investigational when used for all

V. other conditions, including previously treated urothelial carcinoma.

Position Statement

Summary

- Trodelvy (sacituzumab govitecan-hziy) is a Trop-2-directed antibody and topoisomerase inhibitor conjugate that binds to Trop-2-expressing cancer cells and causes cell death.
- The intent of this policy is to allow coverage of Trodelvy (sacituzumab govitecan-hziy) where it has been shown to be effective, up to the dose shown to be safe and effective in clinical trials (as detailed in the coverage criteria).
- ***Triple-negative breast cancer (TNBC):*** The initial approval of Trodelvy (sacituzumab govitecan-hziy) was based on a single-arm, open-label, basket trial. Subsequently, Trodelvy (sacituzumab govitecan-hziy) was studied in a multicenter, open-label, randomized Phase 3 trial in patients with relapsed advanced TNBC after two prior standard (cytotoxic) chemotherapy regimens in the advanced setting. Despite the limited evidence, given the context in which it has been studied as salvage therapy, Trodelvy (sacituzumab govitecan-hziy) may offer value in this salvage clinical setting when standard therapies for advanced TNBC are exhausted. Recently, the NCCN added a recommendation for the use of Trodelvy (sacituzumab govitecan-hziy) in the second-line setting for mTNBC. However, the recommendation is not supported by the clinical trial evidence, as the trial required two prior regimens.
- ***Hormone-receptor (HR)-positive, human epidermal growth factor 2 (HER2)-negative breast cancer:*** The approval of Trodelvy (sacituzumab govitecan-hziy) in pretreated, unresectable locally advanced or metastatic HR-positive, HER2-negative breast cancer was based on one open-label, randomized controlled trial. The use of Trodelvy (sacituzumab govitecan-hziy) as monotherapy was found to improve overall survival (OS) relative to single-agent chemotherapy in patients whose disease had progressed after endocrine therapies, CDK4/6 inhibitors, and cytotoxic chemotherapy (which included a prior taxane-based regimen, and at least one other regimen administered in the metastatic disease setting).
- The use of Trodelvy (sacituzumab govitecan-hziy) is associated with significant side effects, which may limit clinical utility.
- The NCCN guideline lists Trodelvy (sacituzumab govitecan-hziy) among many other potential therapies for advanced TNBC and HR-positive, HER2-negative advanced breast cancer.
- The use of Trodelvy (sacituzumab govitecan-hziy) is considered investigational for all other uses, including previously treated advanced urothelial cancer (FDA indication withdrawn due to failed confirmatory trial).

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit

relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.

- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy

Triple-Negative Breast Cancer (TNBC)

- The initial efficacy of Trodelvy (sacituzumab govitecan-hziy) for FDA approval in mTNBC was based on a multicenter, phase 1/2, open-label, single-arm, basket-trial. [1]
    * Patients had at least two prior systemic regimens in the metastatic setting (median of 3) and ~70% had prior platinum (carboplatin or cisplatin).
    * At the time of data cutoff used for the FDA review, the median duration of follow-up was 9.7 months. Approximately one-third of patients demonstrated an objective response rate (ORR), and 2.8% of patients achieved a complete response.
    * While an ORR was observed, ORR is a surrogate endpoint which has not been shown to reliably predict clinically relevant outcomes such improved overall survival (OS). The lack of clinically meaningful outcomes such as OS makes interpretation of ORR difficult.
- Subsequently, a multicenter, open-label, randomized Phase 3 trial, studied Trodelvy (sacituzumab govitecan-hziy) in patients with unresectable locally advanced or mTNBC, relapsed to at least two prior standard (cytotoxic) chemotherapy regimens [ASCENT]. [2]
    * Patients had relapsed after at least two prior standard chemotherapy regimens for breast cancer (one of which could be in the neoadjuvant or adjuvant setting). Previous therapy had to include a taxane (for any indication). Of the 468 enrolled patients, prior treatments included cytotoxic chemotherapy with taxanes (100%), anthracyclines (82%), cyclophosphamide (82%), carboplatin (66%), and capecitabine (65%). PARP inhibitors (7%) were counted as a prior "chemotherapy regimen" in patients with a documented BRCA1/BRCA2 germline mutation.
    * Patients were randomized to sacituzumab govitecan or physician's choice of single agent chemotherapy (eribulin, capecitabine, gemcitabine, or vinorelbine).
    * The median overall survival (OS) was 12.1 months in the sacituzumab govitecan treatment group and 6.7 months in the chemotherapy treatment group.

- The National Comprehensive Cancer Network (NCCN) guidelines for the management of recurrent or mTNBC breast cancer recognizes Trodelvy (sacituzumab govitecan-hziy) among many potential treatment options in the advanced setting. It is listed as a lower-level recommended treatment option meaning the quality of evidence is low, but there was a consensus among oncologists on the panel for inclusion on the guideline. [4]

Advanced HR-Positive, HER2-Negative Breast Cancer

- The safety and efficacy of Trodelvy (sacituzumab govitecan-hziy) was evaluated in an open-label, randomized controlled trial (TROPiCS-02) in women (N=543) with HR-positive, HER2-negative unresectable or metastatic breast cancer who had progression of disease on or after at least two, but no more than four prior systemic chemotherapy regimens in the metastatic setting. [3]
    * All women had prior anticancer endocrine therapy, a CDK4/6 inhibitor, and at least two prior cytotoxic chemotherapy regimens, at least one of which included a taxane, and at least one of which was administered in the metastatic disease setting. Hormone-targeted therapies [anticancer endocrine therapy and CDK4/6 inhibitors] were not considered as prior systemic chemotherapy treatments.
    * Of the 543 enrolled patients, prior treatments included cytotoxic chemotherapy with taxanes (100%), capecitabine (85%), anthracyclines (84%), cyclophosphamide (76%), eribulin (36%), and fluorouracil (26%). Nearly all patients had at least two prior systemic chemotherapy regimens, with thirty-eight percent of patients had two prior systemic chemotherapy regimens, and 58% had three or more prior chemotherapy regimens).
    * Ninety-five percent of enrolled patients had visceral metastasis.
    * Trodelvy (sacituzumab govitecan-hziy) was administered every 21 days until disease progression. It was compared with physician's choice of single-agent chemotherapy which could have included eribulin, capecitabine, gemcitabine, or vinorelbine.
    * Prior treatment with a topoisomerase 1 inhibitor (e.g., irinotecan, topotecan) was not allowed as Trodelvy (sacituzumab govitecan-hziy) delivers a topoisomerase 1 inhibitor payload.
    * Median OS was 14.4 months and 11.2 months in the Trodelvy (sacituzumab govitecan-hziy) and single-agent chemotherapy treatment arms, respectively. This difference is both statistically significant and clinically relevant.
- The NCCN breast cancer guideline lists Trodelvy (sacituzumab govitecan-hziy) as a treatment option for patients who have received prior endocrine therapy, a CDK4/6 inhibitor, and at least two lines of prior chemotherapy, one of which was a taxane, and at least one of which was in the metastatic setting. [4]

Investigational Uses

Advanced Urothelial Cancer (UC)

The use of Trodelvy (sacituzumab govitecan-hziy) for treatment of previously treated advanced UC is considered 'investigational,' as the confirmatory trial failed to meet the endpoint of overall survival and the FDA indication was withdrawn.

- Trodelvy (sacituzumab govitecan-hziy) was initially approved for previously treated advanced UC based on a single-arm, multicenter Phase 2 trial (TROPHY-U-01) via the Accelerated Approval pathway. [5]
- Subsequently, the confirmatory trial (TROPICS4) failed to demonstrate an overall survival improvement as compared to standard subsequent-line chemotherapy. [6] As a result, the manufacturer voluntarily removed the FDA indication. [7,8]

Safety [9]

- The most common adverse events (incidence of 25% or more) reported with Trodelvy (sacituzumab govitecan-hziy) include nausea, neutropenia, diarrhea, fatigue, anemia, vomiting, alopecia, constipation, rash, decreased appetite, and abdominal pain. [1]
- Trodelvy (sacituzumab govitecan-hziy) has a Boxed Warning for neutropenia and diarrhea.

Dosing [9]

- The recommended dose of Trodelvy (sacituzumab govitecan-hziy) is 10 mg/kg administered as an intravenous infusion once weekly on days 1 and 8 of 21-day treatment cycles for all indications.

Appendix 1: Cytotoxic Chemotherapy Agents Used in the Treatment of Advanced Breast Cancer [4] a,b,c

"Preferred" Single Agents	***Chemotherapy Combinations***
Anthracyclines	AC: doxorubicin/cyclophosphamide
doxorubicin (generic, Adriamycin)	EC: epirubicin/cyclophosphamide
doxorubicin liposomal (generic, Doxil)	CMF: cyclophosphamide/methotrexate/fluorouracil
Taxanes	docetaxel/capecitabine
paclitaxel (generic Taxol)	GT: gemcitabine/paclitaxel
Anti-metabolites	gemcitabine/carboplatin
capecitabine (generic, Xeloda)	paclitaxel/bevacizumab
gemcitabine (generic, Gemzar)	carboplatin + paclitaxel or albumin-bound paclitaxel
Other microtubule inhibitors	
vinorelbine (generic, Navelbine)	
eribulin (generic, Halaven)	
"Other" Single Agents	
cyclophosphamide (generic, Cytoxan)	cisplatin
carboplatin	epirubicin
docetaxel (generic, Taxotere)	Ixempra (ixabepilone)
Abraxane (nab-paclitaxel)	Trodelvy (sacituzumab govitecan-hziy; for TNBC)

[a] Hormone-targeted therapies (endocrine therapy and CDK4/6s) are not considered "cytotoxic chemotherapy."

[b] PARP inhibitors may be counted as a prior "chemotherapy regimen" in patients with a documented BRCA1/BRCA2 germline mutation. [3]

[c] Neoadjuvant/adjuvant regimens are not included, as finite regimens used for non-advanced disease. Examples: ddAC+T [doxorubicin/cyclophosphamide followed by paclitaxel], TC [docetaxel/ cyclophosphamide], or carboplatin/paclitaxel/pembrolizumab followed by AC/pembrolizumab.

Appendix 2: Endocrine Therapies Used in HR-Positive Advanced Breast Cancer		
Aromatase inhibitors (AIs)	**Selective estrogen receptor degraders (SERDs)**	**Selective estrogen receptor modifiers (SERMs)**
Arimidex (anastrozole)	Orserdu (elacestrant)	tamoxifen (Nolvadex, Soltamox)
Aromasin (exemestane)	Faslodex (fulvestrant)	
Femara (letrozole)		

Appendix 3: CDK4/6 Inhibitors Used in HR-Positive Advanced Breast Cancer
Verzenio (abemaciclib)
Ibrance (palbociclib)
Kisqali (ribociclib)

Cross References
Abraxane, nab-paclitaxel (a.k.a. albumin-bound paclitaxel, paclitaxel albumin-stabilized nanoparticle formulation, ABI-007), Medication Policy Manual, Policy No. dru310
CDK 4/6 Inhibitors for breast cancer, Medication Policy Manual, Policy No. dru611

Codes	Number	Description
HCPCS	J9317	Injection, sacituzumab govitecan-hziy (Trodelvy), 2.5 mg

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Revision History

Revision Date	Revision Summary
3/6/2025	• Added to Investigational Uses: previously treated advanced urothelial carcinoma, due to FDA withdrawal of this indication (previously "not medically necessary"). • Clarified language for step therapy with cytotoxic chemotherapy for HER2-negative breast cancer [no change to intent].
12/12/2024	Removed coverage of previously treated advanced urothelial carcinoma due to manufacturer withdrawal of indication.
6/20/2024	Simplification of step therapy for HER2-negative breast cancer criteria (TNBC and HR-positive, HER2-negative). No change to overall intent of coverage criteria.
9/14/2023	Added "locally advanced" verbiage to coverage criteria for unresectable locally advanced or metastatic HR-positive, HER2-negative breast cancer for clarity. No change to intent.
6/15/2023	Added coverage for a new indication in unresectable locally advanced or metastatic HR-positive, HER2-negative breast cancer after prior endocrine therapy, CKK4/6 inhibitor therapy, and at least two prior lines of chemotherapy which must have included a taxane, and at least one of which was administered in the metastatic setting.
6/17/2022	No criteria changes with this annual update.
10/15/2021	Added coverage for new indication in advanced urothelial cancer.
7/16/2021	Updated diagnosis criterion from "metastatic triple-negative breast cancer" to "advanced triple-negative breast cancer" based on FDA indication update.
1/20/2021	Removed platin requirement from coverage criteria.
7/22/2020	New policy (effective 8/15/2020). The intent of this policy is to allow coverage of Trodelvy (sacituzumab govitecan-hziy) where it has been shown to be effective, up to the dose shown to be safe and effective in clinical trials

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Medication Policy Manual **Policy No:** dru648

Topic: Medications for thrombocytopenia **Date of Origin:** October 1, 2020

- Alvaiz (eltrombopag)
- Doptelet, avatrombopag
- Mulpleta, lusutrombopag
- Nplate, romiplostim
- Promacta, eltrombopag
- Tavalisse, fostamatinib

Committee Approval Date: June 20, 2024 **Next Review Date:** 2025

Effective Date: September 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

This policy is for specific medications used in the treatment of thrombocytopenia, both oral and injectable.

PLEASE NOTE: For IVIG coverage requirements, see the IVIG-specific medication policy (dru020).

Policy/Criteria

Most contracts require pre-authorization approval of medications for thrombocytopenia prior to coverage.

I. Continuation of therapy (COT): Medications for thrombocytopenia may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, full policy criteria must be met for coverage.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve): Medications for thrombocytopenia may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that one of the following criterion A through E below are met.

A. **Chronic idiopathic thrombocytopenia** (ITP), also known as "immune thrombocytopenia," when criteria 1, 2, and 3 below are met:

For Doptelet (avatrombopag), Nplate (romiplostim), Promacta (eltrombopag), Tavalisse (fostamatinib), and Alvaiz (eltrombopag) Only:

1. The diagnosis of **chronic ITP** has been made by, or in consultation with, a specialist in hematology.

AND

2. The patient is at risk of spontaneous bleeding as demonstrated by either one of the following criteria (a or b) below:

a. Platelet count less than 20 x 10^9/L.

OR

b. Platelet count less than 30 x 10^9/L accompanied by symptoms of bleeding.

AND

3. Prior treatment with an adequate course of systemic corticosteroids (e.g., prednisone 1 to 2 mg/kg for 2 to 4 weeks, or pulse dexamethasone 40 mg daily for 4 days).

OR

B. **Thrombocytopenia in adult patients with chronic liver disease** (CLD) who are scheduled to undergo a procedure when criteria 1 through 4 below are met.

For Doptelet (avatrombopag) and Mulpleta (lusutrombopag) Only:

1. A diagnosis of **thrombocytopenia** and **chronic liver disease** (CLD) established by or in consultation with a specialist in hematology or hepatology.

AND

2. Platelet count less than 50 x 10^9/L.

AND

3. Planned invasive procedure within the next 14 days.

AND

4. **Mulpleta (lusutrombopag) Only*:*** Treatment with Doptelet (avatrombopag) was not effective, not tolerated or use is contraindicated.

OR

C. **Thrombocytopenia associated with hepatitis C** (HCV) when criterion 1 below is met.

For Promacta (eltrombopag) and Alvaiz (eltrombopag) Only:

1. A diagnosis of **thrombocytopenia** associated with **hepatitis C** (HCV) and the patient is unable to initiate or maintain interferon (IFN) therapy due to platelet count less than 75 x 10^9/L, and a Child-Pugh level A (score 5-6) (see *Appendix A*).

OR

D. **Severe aplastic anemia** when criteria 1, 2, and 3 below are met:

For Promacta (eltrombopag) and Alvaiz (eltrombopag) Only:

1. The diagnosis of **severe aplastic anemia** has been made by, or in consultation with a specialist in hematology.

AND

2. Documentation of a baseline severe cytopenia (severe aplastic anemia), with **at least two** of the following three criteria:

a. Reticulocyte count less than 20 x 10^9/L

b. Platelet count less than 20 x 10^9/L

c. Absolute neutrophil count (ANC) less than 500 cells/mm^3

AND

3. Baseline platelet count of less than 30,000/mm^3.

OR

E. **Hematopoietic syndrome of acute radiation syndrome (HSARS)** when criterion 1 below is met:

For Nplate (romiplostim) Only:

1. A diagnosis of **hematopoietic syndrome** of **acute radiation syndrome**.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Nplate (romiplostim) coverable only under the medical benefit (as a provider-administered medication).

B. Regence Pharmacy Services considers all oral medications coverable only under the pharmacy benefit (as self-administered medications).

C. When pre-authorization is approved, medications for thrombocytopenia will be authorized in quantities and authorization periods as listed in Table 1.

TABLE 1.

Quantity Limit	Initial:	Re-authorization:
Chronic ITP		
Doptelet (avatrombopag): Up to 40 mg per day. **Promacta (eltrombopag):** Up to 75 mg per day. **Tavalisse (fostamatinib):** Up to 300 mg per day. **Nplate (romiplostim):** Up to 10 mcg/kg/dose per week. **Alvaiz (eltrombopag):** Up to 54 mg per day.	12 weeks	Continued authorization (after the initial 12-week period) **shall** be reviewed at least annually to confirm that current medical necessity criteria are met, the dose is within the dose limits, and that the patient's recent (within the last 90 days) platelet count is either: **1.** Equal to or greater than 30 x 10^9/L but not more than 150 x 10^9/L. **OR** **2.** Less than 30 x 10^9/L but platelet counts have increased from baseline accompanied with a resolution of previous bleeding.
CLD, scheduled to undergo a procedure		
Doptelet (avatrombopag): 15 tablets per treatment course. **Mulpleta (lusutrombopag)**: 7 tablets per treatment course.	One treatment course	No reauthorization. Apply Initial authorization criteria for any additional procedures.
Thrombocytopenia associated with HCV		
Promacta (eltrombopag): Up to 100 mg per day. **Alvaiz (eltrombopag):** Up to 72 mg per day.	12 weeks	Continued authorization (after the initial 12-week period) **shall** be reviewed at least annually to confirm that current medical necessity criteria are met, the dose is within the dose limits, and the patient remains on interferon/ribavirin therapy and platelet count is less than 400 x 10^9/L.

Quantity Limit	Initial:	Re-authorization:
Severe aplastic anemia		
Promacta (eltrombopag): Up to 150 mg per day. **Alvaiz (eltrombopag):** Up to 108 mg per day.	16 weeks	The patient has a documented hematologic response, based on blood counts AND/OR a reduced need for blood products as defined below. **<u>Initial Reauthorization:</u>** Initial authorization **shall** be reviewed at 16 weeks. Ongoing coverage requires the patient's recent (within the last 90 days) blood counts and that the patient has a demonstrated hematologic response, defined as one of the following (a through d). The documented baseline cytopenia and/or transfusion needs will be used for demonstration of hematologic response. If initial reauthorization is approved, a subsequent 16-week period will be authorized. **a.** Platelet count equal to or greater than 30 x 10^9/L but not more than 150 x 10^9/L AND transfusion independence (no blood product transfusions given) for 8 consecutive weeks. **OR** **b.** Platelet count less than 30 x 10^9/L but 20 x 10^9/L more than baseline. **OR** **c.** Reduction in RBC transfusions (of at least 4 units) for 8 consecutive weeks or hemoglobin increase of at least 1.5 g/dL from baseline. **OR** **d.** Absolute neutrophil count (ANC) increase of 100% from baseline or an ANC increase greater than 500/mm^3. **<u>Continued Authorization:</u>** Continued authorization (following the initial combined 32-week period) **shall** be reviewed at least annually to confirm that current medical necessity criteria are met, the dose is within the dose limits, and there is documentation of recent blood counts/transfusion records (within the last 90 days) that the patient is able to maintain blood counts or ongoing reduced need for blood products, as defined in the initial re-authorization above.
Hematopoietic syndrome of acute radiation syndrome		
Nplate (romiplostim): Up to 10 mcg/kg/dose	One treatment course	No reauthorization. Apply Initial authorization criteria for any additional exposures.

IV. Medications for thrombocytopenia are considered investigational when used for all other conditions, including but not limited to:

A. Acute thrombocytopenia.

B. Low platelet counts secondary to other conditions or diseases [including, but not limited to, cancer, HIV, and myelodysplastic syndrome (MDS)], except as listed in the coverage criteria.

C. Drug-induced thrombocytopenia [e.g., chemotherapy, heparin (HIT)], except as listed in the coverage criteria.

D. Thrombocytopenia secondary to disseminated intravascular coagulation, hemangiomas, or platelet loss (massive bleeding).

E. Thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome (TTP/HUS).

F. Pancytopenia (other than aplastic anemia).

G. *For Promacta (eltrombopag) and Alvaiz (eltrombopag):* Use in combination with ATG (or within 4 months) for aplastic anemia.

H. *For Tavalisse (fostamatinib):* Rheumatoid arthritis.

Position Statement

Summary

- The intent of this policy is to cover medications for thrombocytopenia (as listed in Table 1) for the indications and dose for which they have been shown to be safe and effective, as detailed in the coverage criteria above:
  - * Chronic idiopathic thrombocytopenia (ITP), when traditional first line therapies are ineffective or not a treatment option, as detailed in the coverage criteria.
  - * Aplastic anemia, when traditional first line therapies are ineffective or not a treatment option, as detailed in the coverage criteria [*Promacta (eltrombopag) and Alvaiz (eltrombopag) only*].
  - * Patients with hepatitis C virus (HCV), when the patient is unable to remain on interferon (IFN) therapy due to thrombocytopenia [*Promacta (eltrombopag) and Alvaiz (eltrombopag) only*].
  - * Prior to a planned invasive procedure in patients with chronic liver disease (CLD) and significant thrombocytopenia [*Doptelet (avatrombopag) and Mulpleta (lusutrombopag) only*].
  - * Hematopoietic Syndrome of Acute Radiation Syndrome [*Nplate (romiplostim) only*].
- Medications for thrombocytopenia (as listed in Table 1) in this policy include:
  - * Thrombopoietin receptor agonists (TPO RAs): Nplate (romiplostim), Promacta (eltrombopag), Doptelet (avatrombopag), Mulpleta (lusutrombopag), and Alvaiz (eltrombopag).
  - * Kinase inhibitor: Tavalisse (fostamatinib).

* Alvaiz (eltrombopag) is the choline salt form of eltrombopag, whereas Promacta (eltrombopag) is the olamine salt form of eltrombopag. Alvaiz (eltrombopag) has demonstrated bioequivalency to Promacta (eltrombopag) and is considered a pharmaceutical alternative (not generic) to Promacta (eltrombopag). The effectiveness of Alvaiz (eltrombopag) for its FDA- approved indications was based on clinical trials of Promacta (eltrombopag) and an additional study to establish its bioequivalency to Promacta (eltrombopag).

Chronic ITP

- Medications for thrombocytopenia used for ITP [Doptelet (avatrombopag), Nplate (romiplostim), Promacta (eltrombopag), Alvaiz (eltrombopag), Tavalisse (fostamatinib)] have only been studied in patients for whom traditional treatments have been ineffective. Current guidelines recommend steroids as a first-line treatment for ITP. Splenectomy (a surgical treatment option), rituximab, and TPO RAs are among recommended treatment options for refractory chronic ITP. Splenectomy and rituximab can put patients into long-term clinical remission. TPO RAs on the other hand, must be dosed continually to see benefit. [1]
- The safety and efficacy of TPO RAs or Tavalisse (fostamatinib) used for ITP were established in placebo-controlled trials in patients with low platelet counts despite at least one prior treatment for ITP.
- There are no clinical trials that have demonstrated a superior benefit of TPO RAs or Tavalisse (fostamatinib) over therapies such as corticosteroids, immunoglobulin, splenectomy, rituximab, or thrombopoietin receptor agonists.

Thrombocytopenia associated with HCV

- Eltrombopag is also used to treat thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. Safety and efficacy of eltrombopag has not been established for use in combination with direct-acting antivirals, such as protease inhibitors or polymerase inhibitors. [2 3]

Aplastic anemia

- Aplastic anemia is a rare, life-threatening condition, characterized by trilineage bone marrow hypoplasia, which leads to anemia, neutropenia, and thrombocytopenia.[4-7]
    * Aplastic anemia is usually treatable with allogeneic stem cell transplantation (HSCT), the only curative therapy, or immunosuppression therapy (IST) of antithymocyte globulin (ATG) with cyclosporine. Response to IST is delayed, usually three to four months; therefore, ongoing support of cytopenias is expected.
    * There is no standard therapy for refractory aplastic anemia patients who are unable to undergo a HSCT. Treatment is generally supportive with red cell and platelet transfusions and treatment of infections but may include eltrombopag as a treatment option.
    * In clinical trials, hematologic response to eltrombopag was based on improvement in blood counts and/or a reduced need for blood products. A patient's baseline cytopenia(s) and/or transfusion dependence must be considered when evaluating response to eltrombopag and the need for continued therapy.

Chronic Liver Disease (CLD), scheduled to undergo a procedure

- The safety and efficacy of both Doptelet (avatrombopag) and lusutrombopag in patients with CLD who were scheduled to undergo a procedure was established in two placebo-controlled trials. The trials evaluated a reduction in platelet transfusions or rescue therapy; however, reductions in bleeding rates were not assessed. [8]
- There are no trials comparing Doptelet (avatrombopag) or Mulpleta (lusutrombopag) to each other or any other medication or treatment for CLD associated thrombocytopenia. There is no evidence that one is superior to one another in terms of safety or efficacy; however, Doptelet (avatrombopag) is the lowest cost.
- "Medications for thrombocytopenia" may be covered for up to the doses shown to be safe and effective in clinical trials, as detailed in the coverage criteria above.
- There is insufficient evidence to support the safety or efficacy of "medications for thrombocytopenia" in any other condition or type of thrombocytopenia, including chemotherapy-induced thrombocytopenia, except as listed in the coverage criteria.

Clinical Efficacy

<u>Refractory ITP</u>

- Avatrombopag was studied in one small, phase 3, randomized, double-blind, placebo-controlled trial in patients with ITP refractory to one or more ITP therapies (corticosteroids, immunoglobulins, azathioprine, danazol, cyclophosphamide, rituximab).[8]
    * Patients had a baseline platelet count of less than 30 x 10^9/L.
    * Although the study demonstrated that avatrombopag improves platelet levels compared to placebo, its effect on more clinically meaningful outcomes (e.g., overall survival, decreased incidence of bleeding, need for rescue therapies) is unknown.
- Tavalisse (fostamatinib) was studied in two phase 3, randomized, double-blind, placebo-controlled trials in patients with ITP refractory to one or more ITP therapies (including corticosteroids, immunoglobulins, splenectomy, rituximab or a TPO RA). Patients were allowed to continue with their stable concurrent ITP therapy. [9]
    * The primary endpoint was a stable platelet response (defined as platelets ≥50 x 10^9/L).
    * In the first trial, significantly more patients achieved a stable platelet response when treated with fostamatinib compared to placebo. In the second trial, the difference in stable platelet response was numerically greater, but did not reach statistical significance. Although increases in platelet count were observed in clinical trials, it is unknown how platelet response correlates to more clinically meaningful outcomes (e.g., overall survival, decreased incidence of bleeding).
- Romiplostim has been proven in clinical studies to be more effective for increasing platelets than placebo. [1 11]
    * For every two non-splenectomized patients who received romiplostim, one patient-maintained platelet counts above 50 x 10^9/L for 6 weeks during the last 8 weeks of the trial.

    * For every three splenectomized patients who received romiplostim, one patient-maintained platelet counts above 50 x 10^9/L for 6 weeks during the last 8 weeks of the trial.

- Eltrombopag has been proven in clinical studies to be more effective for increasing platelets than placebo. [1 11]
    * Eltrombopag may increase platelet counts; however, its effectiveness past 6 months is uncertain.
    * Because the risk of bleeding is only prominent when platelet count drops below 20 x 10^9/L, it is difficult to quantify the clinical benefit of treatment when half of the patients in the studies had platelet count above 20 x 10^9/L at baseline.
- It is uncertain whether the increase in platelets with "medications for ITP" is sustainable long term (beyond 24 to 52 weeks) and whether "medications for ITP" decreases bleeding episodes or other complications in patients with chronic ITP. Effect on overall survival is unknown, given the lack of evidence. [11] Overall, long term data are lacking.
- Standard of care therapies are effective for many patients with chronic ITP.
    * Around one-third of patients may expect a long-term response from treatment with an oral corticosteroid. Corticosteroids should be rapidly tapered and stopped in patients who fail to respond after 4 weeks.[1]
    * Up to two-thirds of patients with ITP who undergo splenectomy may achieve a normal platelet count, which is often sustained with no additional therapy. [1]
- Principles of treatment for ITP
    * A normal platelet count in a healthy person is between 150 x 10^9/L and 400 x 10^9/L. The goal of treatment for chronic ITP should be to maintain a safe platelet count, not to achieve a normal platelet count.[1]
    * Choosing Wisely, an evidence-based initiative to promote wise use of medical resources, states that patients with ITP should not be treated in the absence of bleeding or a very low platelet count. Only rarely should patients be treated when platelet counts are above 30 x 10^9/L, such a preparation of surgery or an invasive procedure. Unnecessary treatment exposes patients to potential adverse events and raises the overall cost of care, with unknown clinical benefit.
    * The risk of bleeding and mortality increases as platelet counts drops below 20 or 30 x 10^9/L. but there are large individual variations. [14 15]
    * Taking in to account the slow time to response of TPO receptor agonists or TKIs and frequent platelet lability in refractory ITP patients, ongoing use of medications for ITP may be needed for patients with platelets well above the critical threshold, such as over 30 x 10^9/L but less than 150 x 10^9/L.
- There are no studies evaluating the efficacy of "medications for ITP" compared to other refractory ITP treatment options. Trials of "medications for ITP" were conducted in patients refractory to standard treatments, such as corticosteroids, immunoglobulins, rituximab, cytotoxic therapies, danazol, and azathioprine.

Thrombocytopenia in HCV

- Two randomized-controlled studies for the treatment of thrombocytopenia in adult patients with chronic hepatitis C compare eltrombopag to placebo. Eltrombopag was administered in combination with pegylated interferon and ribavirin for up to 48 weeks. The primary efficacy endpoint for both trials was sustained virologic response (SVR) defined as the percentage of patients with undetectable HCV-RNA at 24 weeks after completion of antiviral treatment. The median time to achieve the target platelet count ≥90 x 10^9/L was approximately 2 weeks. Ninety-five percent of patients were able to initiate interferon therapy. In both trials, a significantly greater proportion of patients treated with eltrombopag achieved SVR.
- Eltrombopag was only studied in patients trying to receive interferon therapy.
    * There is no data on the safety and efficacy of eltrombopag in HCV patients on direct-acting antivirals.
    * There is insufficient evidence to support the use of eltrombopag in patients with thrombocytopenia associated with chronic liver disease (CLD), in the absence of trying to initiate and maintain interferon therapy for HCV. This includes CLD patients with liver failure and/or cirrhosis and patients undergoing an invasive procedure. [8,9]
- Eltrombopag doses should be lowered when platelet levels are between 200 x 10^9/L and 400 x 10^9/L and stopped when platelets are over 400,000 x 10^9/L. [1]

Chronic Liver Disease (CLD)

- Avatrombopag was studied in two phase 3, randomized, double-blind, placebo-controlled, clinical trials (ADAPT-1 and ADAPT-2) in patients with chronic liver disease and platelet counts less than 50 x 10^9/L who were scheduled to undergo an invasive procedure. [8]
    * The studies found that significantly more patients treated with avatrombopag did not require a platelet transfusion or rescue therapy for bleeding up to 7 days after the scheduled procedure compared to patients treated with placebo.
    * In addition, more patients across both trials achieved the target platelet count of ≥50 x10^9/L on the day of the procedure.
- Lusutrombopag was evaluated in two phase 3, randomized, double-blind, placebo-controlled trials (L-PLUS 1 and L-PLUS 2) in patients with chronic liver disease and platelet counts less than 50 x 10^9/L who were scheduled to undergo an invasive procedure.
    * In both trials, a greater proportion of patients who received lusutrombopag did not require a platelet transfusion prior to the primary procedure compared to the placebo treatment group.
    * Additionally, in L-PLUS 2 a higher proportion of patients treated with lusutrombopag did not require rescue therapy from bleeding compared to the placebo treatment group.

Aplastic Anemia

- One non-randomized, open-label single-arm study evaluated the use of eltrombopag in combination with immunosuppressive therapy (ATG plus cyclosporine) as first-line treatment in 92 patients with severe aplastic anemia. [17]
    * Efficacy was established on the basis of complete hematological response at 6 months. A complete response was defined as hematological parameters meeting all 3 of the following values on 2 consecutive serial blood count measurements at least one week apart: absolute neutrophil count (ANC) > 1,000/mcL, platelet count > 100 x 10^9/L and hemoglobin > 10 g/dL.
    * At six months 38 people (44%) of patients had a complete response. The overall and complete hematological response rates at Year 1 (N=78) are 56.4% and 38.5% and at Year 2 (N=62) are 38.7% and 30.6%, respectively.
- One non-randomized, open-label single-arm study evaluated the use of eltrombopag in 43 adult patients with severe aplastic anemia refractory to immunosuppressive therapy (ATG plus cyclosporine). [3 4]
    * All patients had a confirmed diagnosis of severe aplastic anemia, prior use of ATG with cyclosporine, and a baseline platelet count of ≤ 30 x 10^9/L.
    * Eltrombopag was initiated at 50 mg per day for up to 12 weeks. Doses were titrated by 50 mg per day every 2 weeks, up to a maximum of 150 mg per day.
    * The primary efficacy endpoint was hematologic response, defined as a clinically significant change in blood counts or transfusion independence (uni- or multilineage response) at 12 weeks. Response was defined as at least of the following criteria:
        1. Platelet response: increases ≥ 20 x 10^9/L from baseline, or stable platelet counts with transfusion independence for ≥ 8 weeks.
        2. Erythroid response (if HgB < 9 at baseline): Hemoglobin increase ≥1.5 g/dL, or a reduction in greater than or equal to 4 units of RBC transfusions for 8 consecutive weeks.
        3. Neutrophil response (if ANC<500 at baseline): ANC increase of 100% or an ANC increase ≥ 500.
    * Eltrombopag was discontinued after 16 weeks if no hematologic response was observed. Patients who responded continued therapy in an extension phase of the trial.
    * Forty percent of patients (17 of 43 patients) demonstrated a hematologic response in at least one lineage. One response had a trilineage response and four had a bi lineage response. The median time to initial hematologic response was approximately 12 weeks (range 8-14 weeks).
- Aplastic anemia is a rare, life-threatening condition, characterized by trilineage bone marrow hypoplasia, with low hematopoietic stem and progenitor cells, resulting in low red blood cell, white blood cell, and platelet counts (anemia, neutropenia, and thrombocytopenia). [7]

- Aplastic anemia is usually treatable with allogeneic stem cell transplantation (HSCT) or immunosuppression therapy (IST). [7]
    * Early spontaneous recovery is infrequent. Treatment should start as soon as the patient is stabilized, and the diagnosis confirmed.
    * Curative therapy with HSCT is preferred for newly-diagnosed patients less than 40 years of age if they have an appropriate donor.
    * For patients over the age of 40, antithymocyte globulin (ATG) with cyclosporine is recommended, with a 50 to 80% response rate. However, response is delayed and response is generally not seen until three to four months after starting IST. Ongoing transfusion support with packed RBCs and platelets may be needed, along with neutropenic support. Cyclosporin maintenance therapy is used to prevent relapse.
    * Re-treatment with ATG or another immunosuppressant can be considered after a minimum of four months, along with enrollment in a clinical trial. Use of prednisone is not recommended, as they are ineffective and increase the risk of bacterial and fungal infections.
- For patients with aplastic anemia refractory to ATG therapy and those with relapse, standard therapy is allogeneic stem cell transplantation (HSCT). [7]
- There is no standard therapy for refractory aplastic anemia patients who are unable to undergo a HSCT, due to lack of a suitable donor for HSCT (20 to 40% of patients) or other contraindication to HSCT, such as advanced age. [7]
- Treatment is generally supportive with red cell and platelet transfusions and treatment of infections.
    * Repeat immunosuppression can be used as salvage therapy, but with limited efficacy and significant toxicity.
    * Eltrombopag may be a treatment option for patients with immunosuppression-refractory thrombocytopenia.
- Delayed response to therapy for aplastic anemia is expected, including eltrombopag. [7]
    * Dose titration up to maximum allowed doses may be necessary to achieve a platelet count of $\geq 50 \times 10^9$/L, but effect may take up to 16 weeks. If no effect is seen in 16 weeks, therapy should be stopped.
    * Eltrombopag doses should be lowered when platelet levels are between 200×10^9/L and 400×10^9/L and stopped when platelets are over 400×10^9/L, for a goal of $\geq 50 \times 10^9$/L. Patients who have a complete response should be re-evaluated regularly for the need for ongoing eltrombopag therapy.

<u>Hematopoietic Syndrome of Acute Radiation Syndrome (HS-ARS)</u>

- The evidence for Nplate (romiplostim) for HS-ARS is based on animal studies and previous studies on platelet count in healthy adults. In animal studies, treatment with Nplate (romiplostim) was shown to increase survival compared to supportive therapy alone.[10 18]

- Nplate (romiplostim) may be used after medical or environmental exposure to radiation (e.g. a nuclear explosion, an accident at a nuclear reactor, a radiotherapy accident, or the escape of radioactive waste). [18]

Alvaiz (eltrombopag choline) bioequivalence study to Promacta (eltrombopag olamine)[19]

- An open label, randomized, single dose bioequivalence study was performed to assess the bioequivalence of Alvaiz (eltrombopag choline) 54mg tablets to Promacta (eltrombopag olamine) 75 mg tablets. Subjects received a single dose of either product.
- Plasma concentrations (bioavailability), the key requirement for FDA bioequivalence approval, between the two arms were similar, and both products were found to be safe and well-tolerated. Additional in-vitro studies demonstrated bioequivalence for other tablet strengths; refer to dosing section for details on specific tablet strength bioequivalence.

Laboratory measurement

- Platelet counts are measured per microliter (mcL or µL), which is equivalent to a cubic millimeter (mm^3). The measurement can also be expressed per liter ($x10^9/L$).
- A platelet count of "50" generally refers to a platelet count of 50 x 10^9/L or "50,000 per microliter."
- The following are equivalent expressions of 50,000/µL: "50,000/mm^3" or "50 x 10^9/L."

Safety

- The most common adverse reactions associated with Doptelet (avatrombopag) are pyrexia, abdominal pain, nausea, headache, fatigue, and edema peripheral.
- The most common adverse reaction with Mulpleta (lusutrombopag) is headache.
- The most common adverse reactions associated with Tavalisse (fostamatinib) are diarrhea, hypertension, nausea, respiratory infection, dizziness, increased ALT/AST, rash, abdominal pain, fatigue, chest pain, and neutropenia.
    * Nplate (romiplostim),Promacta (eltrombopag), and Alvaiz (eltrombopag) have a risk of uncommon but serious side effects which need to be weighed against its potential benefit. Due to strict monitoring requirement, safety concerns, and lack of data for self-administration, romiplostim is currently required to be administered by a health professional. Uncommon but serious side effects include:
        * **Bone marrow changes:** romiplostim increases the risk for reticulin deposition within the bone marrow. Clinical studies have not ruled out the possibility that reticulin and other fiber deposition may result in bone marrow fibrosis with cytopenias.
        * **Worsening low blood platelet count**: discontinuation of romiplostim may result in worsened thrombocytopenia than was present prior to romiplostim therapy.
        * **High platelet counts and increased risk of blood clots**: romiplostim may increase platelet counts to a level that produces thrombotic/thromboembolic complications. Portal vein thrombosis has been reported in patients with chronic liver disease taking romiplostim.

    * **Worsening hematologic conditions:** romiplostim may increase the risk for hematological malignancies, especially in patients with myelodysplastic syndrome.
    * **Alvaiz (eltrombopag) and Promacta (eltrombopag) both carry a black boxed warning for the risk of hepatic decompensation in patients with chronic hepatitis C and risk of hepatotoxicity.**
- Patients with chronic liver disease require lower initial dose or Promacta (eltrombopag) and Alvaiz (eltrombopag) due to increased risk for thromboembolic events (specifically portal vein thrombosis).

Dosing

- In refractory ITP, Doptelet (avatrombopag) is taken in doses up to 40mg once daily to maintain a platelet count above $50x10^9$/L.
- In CLD, Doptelet (avatrombopag) is taken 10 to 13 days prior to a scheduled procedure. The recommended dose is 60 mg orally once daily for five days for patients with a platelet count less than 40 x 10^9/L, and 40 mg orally once daily for five days for a platelet count 40 to less than 50 x 10^9/L. The planned procedure is to be 5 to 8 days after the last dose of avatrombopag.
- Mulpleta (lusutrombopag) is started 8 to 14 days prior to a scheduled procedure. The recommended dose is 3 mg orally once daily for 7 days. Patients undergo their procedure 2 to 8 days after the last dose of lusutrombopag.
- In CLD clinical trials with Doptelet (avatrombopag) and Mulpleta (lusutrombopag), platelet counts retuned to baseline levels approximately 30 to 35 days after the last dose. [8]
- The recommended dose of Tavalisse (fostamatinib) is 100 mg orally twice daily. After 4 weeks, the dose is increased to 150 mg twice daily, if needed, to achieve appropriate platelet count levels. The safety and effectiveness of higher doses have not been established.
- Initial dose of romiplostim for ITP is 1 mcg/kg once weekly as a subcutaneous injection. The maximum weekly dose is 10 mcg/kg and adjusted based on clinical response (platelet count and bleeding). Initial response to romiplostim is usually seen within 5 to 14 days, with a peak response in 14 to 60 days. [1]
- The dose of romiplostim for HS-ARS is 10 mcg/kg administered subcutaneously one time. It should be administered as soon as possible after suspected or confirmed radiation exposure. [1]
- Promacta (eltrombopag) may be covered in doses up to 75 mg per day for treatment of ITP, up to 100 mg per day for treatment of thrombocytopenia associated with HCV, and up to 150 mg per day for treatment of severe aplastic anemia, the doses shown to be safe and effective.
    * The initial dose of eltrombopag for most chronic ITP patients (≥ 6 years of age) is 50 mg once daily (25 mg once daily for pediatric patients aged 1 to 5 years). Maximum dose is 75 mg daily and adjusted based on clinical response (platelet count and bleeding).

    * Initial response to eltrombopag for ITP is usually seen within 7 to 28 days, with a peak response in 14 to 90 days. [1]
    * The initial dose of eltrombopag for HCV-associated thrombocytopenia is 25 mg once daily. Maximum dose is 100 mg daily and adjusted based on response of platelet count, to allow initiation of antiviral therapy.
    * The initial dose of eltrombopag for refractory aplastic anemia is 50 mg once daily. For first-line severe aplastic anemia the initial dose is 2.5 mg/kg (in pediatric patients aged 2 to 5 years old), 75 mg (pediatric patients aged 6 to 11 years old), or 150 mg for patients aged 12 years and older with standard immunosuppressive therapy. Maximum dose is 150 mg daily and adjusted based on response of platelet count, to avoid the need for platelet transfusions.

- Alvaiz (eltrombopag) may be covered in doses up to 54mg per day for treatment of ITP, up to 72mg per day for treatment of thrombocytopenia associated with HCV, and up to 108 mg/day for treatment of severe aplastic anemia, the doses shown to be safe and effective.[19]Tablet strength bioequivalence between Alvaiz (eltrombopag choline) and Promacta (eltrombopag olamine) is as follows:

Alvaiz (eltrombopag choline)	Promacta (eltrombopag olamine)
9 mg tablet	12.5 mg tablet
18 mg tablet	25 mg tablet
36 mg tablet	50 mg tablet
54 mg tablet	75 mg tablet

Investigational Uses

- Doptelet (avatrombopag) is also being studied in chemotherapy-induced thrombocytopenia; however, phase 3 trials are ongoing. There is insufficient evidence supporting safety or efficacy of avatrombopag in this setting.[22]
- Although Tavalisse (fostamatinib) is being studied for the treatment of various cancers such as lymphomas, colon cancer, non-small cell lung cancer, and renal cell carcinoma, data is limited to phase 2 trials. There is currently insufficient evidence supporting its safety or efficacy in these settings.
- There is insufficient evidence to establish the safety and efficacy of Tavalisse (fostamatinib) for the treatment of rheumatoid arthritis. While preliminary evidence from phase II trials showed promise, larger phase 3 trials did not support the evidence for safety or efficacy of fostamatinib in rheumatoid arthritis.
- Nplate (romiplostim) has been studied in chemotherapy-induced thrombocytopenia, and is listed in the NCCN guidelines; however, the evidence for support of Nplate (romiplostim) used in this indication is lacking as it is based on poor quality trials that include case series, single center trials, small phase 2 trials and retrospective observational trials that were not randomized. To date, the only improvement shown has

been in the surrogate marker of increased platelet counts. No improvements in overall survival, progression free survival, relapse-rate or non-relapse mortality have been proven. Other proven treatment options currently exist such as platelet transfusions. Therefore, use of Nplate (romiplostim) for chemotherapy-induced thrombocytopenia is considered investigational. [24] [24] [23]

- Although romiplostim and Promacta(eltrombopag) have been studied in a variety of other conditions, including but not limited to the conditions listed below, there is insufficient evidence to support its use in those settings (limited to case reports, retrospective reviews, and Phase 2 trials). Larger, well-designed trials are needed to confirm preliminary results.
    * Acute thrombocytopenia.
    * Low platelet counts secondary to other conditions or diseases, including, but not limited to, cancer, HIV, hepatitis, and aplastic anemia. [3 5]
    * Thrombocytopenia secondary to myelodysplastic syndrome (MDS).
    * Drug-induced thrombocytopenia [e.g., chemotherapy, heparin (HIT)]. [25]
    * Thrombocytopenia secondary to disseminated intravascular coagulation, hemangiomas, or platelet loss (massive bleeding).
    * Thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome (TTP/HUS).

Appendix A: – Child-Pugh Classification of Severity of Liver Disease

Child-Pugh Classification	**Points**		
A: well-compensated disease	5 to 6		
B: significant functional compromise	7 to 9		
C: decompensated disease	10 to 15		
	Points Assigned		
Parameter	**1**	**2**	**3**
Ascites	*Absent*	*Slight*	*Moderate*
Bilirubin (mg/dL)	*< 2*	*2 to 3*	*> 3*
Albumin (g/dL)	*> 3.5*	*2.8 to 3.5*	*< 2.8*
Prothrombin Time			
Seconds over control	*1 to 3*	*4 to 6*	*>6*
INR	*< 1.7*	*1.8 to 2.3*	*> 2.3*
Encephalopathy	*None*	*Grade 1 to 2*	*Grade 3 to 4*

Appendix B: American Society of Hematology – Criteria for the Diagnosis of Chronic Immune Thrombocytopenic Purpura: Diagnosis of Exclusion [3]
- History compatible with the diagnosis of chronic ITP - Normal physical examination findings except for signs of thrombocytopenia (petechiae, purpura, or mucosal bleeding); no adenopathy or splenomegaly - Complete blood count showing isolated thrombocytopenia with large platelets but no anemia unless bleeding or immune hemolysis is present - Bone marrow examination showing normal or increased numbers of megakaryocytes (not required for diagnosis unless unusual manifestation or age >60 yr.) - No clinical or laboratory evidence for other causes of thrombocytopenia

Appendix C: Immunosuppression Therapy for Aplastic Anemia [4]
- Antithymocyte globulin (horse or rabbit) (ATG) with cyclosporine - Anadrol (oxymetholone) - Campath (alemtuzumab)

Cross References
Immune Globulin Replacement Therapy, Medication Policy Manual, Policy No. dru020

Codes	**Number**	**Description**
HCPCS	J2796	Injection, romiplostim (Nplate), 10 micrograms

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Revision History

Revision Date	Revision Summary
6/20/2024	• Added new drug Alvaiz (eltrombopag) to policy; criteria align with criteria for Promacta (eltrombopag). • Updated reauthorization wording in Table 1 for clarity. No change to intent.
6/15/2023	No criteria changes with this annual update.
6/17/2022	Revised reauthorization criteria for ITP from 6 months to 12 months after initial 12-week reauthorization.
7/16/2021	Added coverage criteria for hematopoietic syndrome of acute radiation syndrome (HS-ARS), a newly FDA approved indication.
7/22/2020	• New policy (effective 10/1/2020). Replaces individual drug coverage policies for medications for thrombocytopenia (dru161, dru180, dru560, dru567). • From the individual drug coverage policies: - Step therapy requirements for chronic ITP were revised based on updated guidelines. Step therapy no longer requires splenectomy, IVIG, or rituximab. - Revised quantity limits to align with the maximum dosage for each product. - Updated investigational uses. - No change to intent of coverage for other indications (CLD pre-procedure, HCV-interferon-related, and aplastic anemia). - Revised quantity limits based on current labeling. - Added Continuation of Therapy criteria.

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Medication Policy Manual

Policy No: dru649

Topic: Gaucher Disease Treatments

Date of Origin: October 1, 2020

- Cerdelga (eliglustat)
- Cerezyme (imiglucerase)
- Elelyso (taliglucerase alfa)
- miglustat (generic, Yargesa, Zavesca)
- VPRIV (velaglucerase alfa)

Committee Approval Date: June 20, 2024

Next Review Date: 2025

Effective Date: October 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Gaucher disease is an inherited disorder caused by deficiency of -beta-glucocerebrosidase. Over time, this deficiency causes a buildup of toxic substances in cells which impact the skeleton, bone marrow, spleen, liver, and less commonly the lungs. Cerezyme (imiglucerase), VPRIV (velaglucerase alfa), and Elelyso (taliglucerase alfa) are products that replace the deficient enzyme. Two oral medications, miglustat (generic, Yargesa, Zavesca) and Cerdelga (eliglustat), may also be used in the treatment of Gaucher disease. They act as substrate reduction therapy to reduces the synthesis of GL-1, which accumulates as the result of deficiency of the enzyme glucocerebrosidase.

Policy/Criteria

Most contracts require pre-authorization approval of Gaucher disease treatments prior to coverage.

I. Continuation of therapy (COT): Gaucher disease treatments may be considered medically necessary for COT when criteria A, B, or C, **AND** D **AND** E below are met:

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

AND

D. **For provider-administered medications only:** Site of care administration requirements are met. [refer to Pharmacy Services Medication Policy Manual, Site of Care Review, dru408].

AND

E. "Administration, Quantity Limitations, and Authorization Period" below applies, as well as "Investigational Uses" for combination therapy.

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Gaucher disease treatments may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) confirming that criterion A or B below are met:

A. A diagnosis of **type 1 Gaucher disease** when criteria 1 through 5 below are met:

1. The diagnosis is confirmed by one of the following (a or b):

a. Biochemical assay of glucocerebrosidase activity in white blood cells or skin fibroblasts is less than or equal to 30% of normal activity. (Note: laboratory normal may vary.)

OR

b. Genotyping revealing two pathogenic mutations of the glucocerebrosidase gene.

AND

2. Clinically significant symptoms of the disease are present, such as malnutrition, growth retardation, impaired psychomotor development, anemia, thrombocytopenia, bone disease, hepatomegaly, or splenomegaly.

AND

3. **Miglustat (generic, Yargesa, Zavesca) only:** Enzyme replacement therapy (ERT) is not a therapeutic option (e.g., due to allergy, hypersensitivity, or poor venous access).

AND

4. **Cerdelga (eliglustat) Only:** There is documentation that the member's CYP2D6 metabolizer status (see *Table 2*) is one of the following (a, b, or c):

a. CYP2D6 extensive metabolizer (EM).

OR

b. CYP2D6 intermediate metabolizer (IM).

OR

c. CYP2D6 poor metabolizer (PM).

AND

5. **Cerezyme (imiglucerase), Elelyso (taliglucerase alfa), and VPRIV (velaglucerase alfa) Only:** Site of care administration requirements are met [refer to Medication Policy Manual, Site of Care Review, dru408].

OR

B. **Miglustat (generic, Yargesa, Zavesca) only:** A diagnosis of Niemann-Pick Disease type C.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Cerezyme (imiglucerase), VPRIV (velaglucerase alfa), and Elelyso (taliglucerase alfa) coverable only under the medical benefit (as provider-administered medications).

B. Regence Pharmacy Services considers miglustat (generic, Yargesa, Zavesca) and Cerdelga (eliglustat) coverable only under the pharmacy benefit (as self-administered medications).

C. When pre-authorization is approved, Gaucher disease treatments will be authorized in the following quantities:

TABLE 1.

Product	Quantity Limit
- Cerezyme (imiglucerase) - VPRIV (velaglucerase alfa) - Elelyso (taliglucerase alfa)	• Up to 30 units/kg every 2 weeks (or other equivalent dose). • Doses up to 60 units/kg every 2 weeks may be approved when the patient meets high risk dosing guidelines in *Appendix 1* for adults or *Appendix 2* for children.
- Cerdelga (eliglustat)	• **Extensive metabolizers** or **intermediate metabolizers**: Up to 60 capsules per 30 days. • **Poor metabolizers**: Up to 30 capsules per 30 days.
- Miglustat (generic, Yargesa, Zavesca)	Up to 90 capsules per 30 days.

D. Continued Authorization:

1. Authorization **shall** be reviewed at least annually. Current up to date clinical documentation (including, but not limited to recent chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is still providing clinical benefit, such as disease stability or improvement. This may include, but is not limited to, hematologic indicis, reduction in spleen or liver volume, MRI of spine/femurs, normalized growth, reduced dependency on oxygen, quality of life, and/or plain films of skeleton.

2. **[For Cerezyme (imiglucerase), VPRIV (velaglucerase alfa), and Elelyso (taliglucerase alfa)]:** Doses up to 60 units/kg every 2 weeks may be approved when the physician indicates by chart notes that the patient has not responded to lower doses over a period of 6 months.

PLEASE NOTE: Clinical documentation of response to initial dosing, documentation of the need for dose escalation, as well as subsequent visits for response to dose escalation, should be submitted for review.

IV. Gaucher disease treatments are considered investigational when used in combination with each other.

V. Cerezyme (imiglucerase), VPRIV (velaglucerase alfa), and Elelyso (taliglucerase alfa) are considered investigational when used for all other conditions.

VI. Cerdelga (eliglustat) is considered investigational when used for all other conditions including, but not limited to:

- **A.** Type 1 Gaucher disease with CYP2D6 ultra-rapid metabolizer status or where CYP2D6 metabolizer status cannot be determined.

VII. Miglustat (generic, Yargesa, Zavesca) is considered investigational when used for all other conditions including, but not limited to:

- **A.** Combination use with Cerdelga (eliglustat).
- **B.** Cystic fibrosis.
- **C.** Fabry's Disease.
- **D.** Juvenile GM2 gangliosidosis.
- **E.** Mucopolysaccharidosis.
- **F.** Tay-Sachs disease.

Position Statement

Summary

- Cerezyme (imiglucerase), VPRIV (velaglucerase alfa), and Elelyso (taliglucerase alfa) work by replacing or supplementing the deficient enzyme (i.e., glucocerebrosidase) in order to allow excess material to be degraded.
- Cerdelga (eliglustat) and miglustat (generic, Yargesa, Zavesca) are considered a substrate reduction therapy (SRT) and work by minimizing the amount of GL1 that a cell makes.
- The intent of this policy is to allow coverage of Cerezyme (imiglucerase), VPRIV (velaglucerase alfa), Elelyso (taliglucerase alfa), Cerdelga (eliglustat), or miglustat (generic, Yargesa, Zavesca) for Gaucher disease type 1 in patients with a confirmed diagnosis, symptomatic disease, and other drug-specific criteria as described in the criteria. Miglustat (generic, Yargesa, Zavesca) may also be covered in patients Niemann-Pick Disease type C.
- Enzyme replacement therapy (ERT) with Cerezyme (imiglucerase), Elelyso (taliglucerase alfa), or VPRIV (velaglucerase alfa) is considered the preferred treatment option for all patients with type 1 Gaucher disease requiring pharmacologic treatment. [1,2]

- Treatment should be reserved for symptomatic children (including those with malnutrition, growth retardation, impaired psychomotor development, and/or fatigue), and for adults with symptomatic disease (e.g. platelet count < 60,000/mm^3, liver volume > 2.5 times normal size, spleen volume > 15 times normal size, radiological evidence of skeletal disease). [1]
- Treatment goals are elimination or improvement in symptoms, prevention of irreversible complications, and improvement in the overall health and quality of life. [1]
- ERT has not been shown to improve health outcomes in adult patients with Type 1 Gaucher disease without clinical signs or symptoms of the disease. In addition, ERT does not provide benefit in reversing or decreasing neurologic symptoms associated with Type 2 (acute neuronopathic) or Type 3 (chronic neuronopathic) Gaucher disease. [3]
- The diagnosis of Gaucher disease is usually confirmed by identifying reduced glucocerebrosidase activity in peripheral leukocytes. Targeted DNA analysis to detect the most common mutations is an effective method for confirming the diagnosis. [1]
- SRT with Cerdelga (eliglustat) or miglustat (generic, Yargesa, Zavesca) should not be used in neuronopathic (type 2 or type 3) Gaucher disease and is generally only appropriate for mild systemic disease. [4]
- The addition of miglustat (generic, Yargesa, Zavesca) to ERT has not been shown to provide a substantial benefit over ERT alone. [5]
- CYP enzymes play an important role in the metabolism of Cerdelga (eliglustat) since it is metabolized by the CYP2D6 protein. CYP2D6 genotyping is a simple blood test to determine who is eligible for treatment with Cerdelga (eliglustat) and how often the medication should be given.
- Patients who are CYP2D6 ultra-rapid metabolizers may not achieve adequate concentrations of Cerdelga (eliglustat) to achieve therapeutic effect and a specific dosage cannot be recommended for those patients whose CYP2D6 genotype cannot be determined (indeterminate metabolizers).
- A starting dose of 30 units/kg of body weight every other week is reasonable in the absence of high-risk disease. The mean ERT dose used for long-term therapy in the United States is approximately 30 units/kg every other week. [1,3,6,7]
- Cerezyme (imiglucerase) is approved for doses ranging from 2.5 units/kg three times per week up to 60 units/kg every other week. VPRIV (velaglucerase alfa) and Elelyso (taliglucerase alfa) have been shown to be equivalent to Cerezyme (imiglucerase) on a unit-for-unit basis, and patients switching from Cerezyme (imiglucerase) can be maintained on the same dose. [4,5,6,7,8]
- Cerdelga (eliglustat) is administered orally in doses of 84 mg once or twice daily depending on CYP2D6 metabolizer status and the presence of medications that inhibit the metabolism of eliglustat.
- The addition of miglustat (generic, Yargesa, Zavesca), an oral substrate reduction therapy (SRT) to ERT has not been shown to provide a substantial benefit over ERT alone. [5] However, miglustat (generic, Yargesa, Zavesca) may be an appropriate treatment when ERT is not an option (e.g., allergic hypersensitivity, lack of venous access, patients unwilling to receive intravenous infusions).

- There is no evidence evaluating the addition of Cerdelga (eliglustat) to any ERT product. It is unknown if the combination is safe and effective for Gaucher disease.

Clinical Efficacy

Enzyme Replacement Products

- All ERT products used in the treatment of Gaucher disease have demonstrated improvements in some disease-associated parameters (e.g., hemoglobin level, platelet count, spleen and liver volume). [5]
- In studies of patients with Type 1 Gaucher disease switched from Cerezyme (imiglucerase) to the same dose and frequency of either VPRIV (velaglucerase alfa) or Elelyso (taliglucerase alfa), control of disease parameters such as spleen and liver volume, hemoglobin concentration, and platelet counts were maintained. [5]
- ERT with Cerezyme (imiglucerase) improved quality of life in patients with skeletal manifestations of Gaucher disease as measured by The Short Form-36 Health Survey. [8]
- The U.S. Regional Coordinators of the International Collaborative Gaucher Group (ICGG), a panel of physicians who have extensive experience in the care of Gaucher patients, have made recommendations for therapy and dosing based on risk assessment for irreversible morbid complications (see Appendix 1 and 2). [3,6]
    * Initial doses of ERT of 30-60 units/kg of body weight every other week are considered safe and effective in demonstrating improvements in hepatosplenomegaly, anemia, and thrombocytopenia.
    * Dose adjustments should be based on the patient's initial risk and achievement of therapeutic goals based on individual patient characteristics.
    * The time required to achieve therapeutic goals varies by organ system, but usually requires at least 12 to 36 months.
- The ICGG U.S. Regional Coordinators recommend that all children with Gaucher disease be treated with ERT due to high risk for irreversible, morbid complications. [6,7]
    * Diagnosis of Gaucher disease in the first and second decades of life is indicative of a rapidly progressive course.
    * Early intervention is necessary for these children, during the time when the skeleton is immature, to enable them to attain their peak skeletal mass by early adulthood.

Cerdelga (eliglustat) in Gaucher Disease

- The evidence of efficacy for Cerdelga (eliglustat) is of low quality and is based on two randomized controlled trials.
- Cerdelga (eliglustat) was evaluated versus placebo in 40 treatment naïve, type 1 patients (defined as no SRT within the past six months and no ERT within the last nine months) for percent change in spleen volume from baseline to nine months. [9]
    * At nine months spleen volume had decreased by 27.8% in the Cerdelga (eliglustat) groups versus a 2.3% increase in the placebo group (difference -30.0%; 95% confidence interval: -36.8, -23.2; p-value < 0.0001).

    * This trial was appraised as low confidence due primarily to potential confounding and uncertain generalizability of the results as some patients were treated with a dose of Cerdelga (eliglustat) that is not currently FDA-approved.

- A comparative study evaluated Cerdelga (eliglustat) versus Cerezyme (imiglucerase) in 159 type 1 patients currently receiving ERT. [10]
    * The primary endpoint assessed was a composite of stability in Hgb level (defined as < 1.5 g/dL decrease), platelet count (defined as < 25% decrease), and liver and spleen volume (defined as < 20% and < 25% increase, respectively).
    * At 12 months, 84.8% and 93.6% of patients met the primary endpoint in the Cerdelga (eliglustat) and Cerezyme (imiglucerase) groups, respectively, which met the pre-specified definition for non-inferiority.

miglustat (generic, Yargesa, Zavesca) in Gaucher Disease

- Miglustat (generic, Yargesa, Zavesca) has only been studied in patients with mild-to-moderate symptomatic Gaucher disease. It has not been evaluated for efficacy in patients with severe disease (such as patients with skeletal manifestations, hemoglobin concentrations less than 9 mg/L, and/or platelet counts less than 50 x 10^9/L). [1]
- Two prospective, open-label, non-comparative trials described the safety and efficacy of miglustat (generic, Yargesa, Zavesca) in patients with mild-to-moderate type 1 Gaucher disease. Over a period of 12 to 24 months, miglustat (generic, Yargesa, Zavesca) therapy resulted in improvement in liver and spleen volume, increases in hemoglobin, and stable or improved platelet counts and bone involvement. [11,12]

miglustat (generic, Yargesa, Zavesca) in Niemann Pick Disease Type C

- There is evidence which suggests that miglustat (generic, Yargesa, Zavesca) in doses of 200 mg three times daily improves clinical markers for Niemann-Pick disease type C (NPC) and stabilizes neurological disease progression. Although the small numbers of patients studied and concomitant medications make the results uncertain, patients with NPC have few other treatment options. [13-15]

Investigational Uses

- A small study evaluated the use of miglustat (generic, Yargesa, Zavesca) in the management of five patients with juvenile GM2 gangliosidosis. There was no clear benefit observed, but the study was small and did not include a comparator. Larger, well-designed randomized controlled trials are needed to establish the safety and efficacy of miglustat (generic, Yargesa, Zavesca) in this condition. [16]
- One small, randomized, placebo-controlled, study evaluated the use of miglustat (generic, Yargesa, Zavesca) in patients with Fabry's disease. After 6 months of treatment, miglustat (generic, Yargesa, Zavesca) did not significantly reduce the number of globotriaosylceramide inclusions per kidney interstitial capillary compared to placebo.
- One single-center, placebo-controlled study evaluated the use of miglustat (generic, Yargesa, Zavesca) for improvement in Vineland Adaptive Behavior Scales in patients with mucopolysaccharidosis type III. No improvement or stabilization in behavior was seen in the miglustat (generic, Yargesa, Zavesca) group. [17]

- A small study evaluated the use of miglustat (generic, Yargesa, Zavesca) in the management of late-onset Tay-Sachs disease. Though the study had flaws that make the results uncertain, the study authors concluded that miglustat (generic, Yargesa, Zavesca) did not lead to measurable benefits. [18]
- A small, single-center, double-blind, placebo-controlled study evaluated the use of miglustat (generic, Yargesa, Zavesca) in 11 patients with cystic fibrosis. No statistically significant changes in total chloride secretion, sweat chloride value, or FEV1 were detected. Further study is required to assess any potential benefit of miglustat (generic, Yargesa, Zavesca) in the condition. [19]

Dosing [20]

- Dose adjustments for ERT are made on an individual basis and should consider patient-specific factors.
    * Increases in ERT dose may be necessary to achieve therapeutic goals or for relapse following dose reduction. An increased dose may also be indicated if visceromegaly, anemia, thrombocytopenia, and biomarkers fail to improve after six months of therapy. However, an increased dose is unlikely to reverse certain types of pathology (e.g., osteonecrosis and fibrosis of the liver, spleen, or lung)
- The recommended dosage of miglustat (generic, Yargesa, Zavesca) is 100 mg three times daily. The dose should be reduced in patients with tremor, diarrhea, or renal impairment.
- The recommended dosage of Cerdelga (eliglustat) is 84 mg twice daily in CYP2D6 extensive metabolizers and intermediate metabolizers and 84 mg once daily in CYP2D6 poor metabolizers.
    * Drugs that inhibit CYP2D6 and CYP3A pathways may significantly increase exposure to Cerdelga (eliglustat) and result in cardiac arrhythmias.
    * Co-administration of Cerdelga (eliglustat) with other CYP2D6 and CYP3A inhibitors may require dosage adjustment depending on the CYP2D6 metabolizer status to reduce the risk of potential significant adverse reactions.
    * The following table includes dosing recommendations when Cerdelga (eliglustat) is co-administered with other CYP2D6 and CYP3A inhibitors:

TABLE 2:

CYP450 Inhibitors	Recommended Cerdelga (eliglustat) dosage, by CYP2D6 Status			
	Ultra-Rapid Metabolizer (URM)	Extensive Metabolizer (EM)	Intermediate metabolizer (IM)	Poor metabolizer (PM)
Strong or moderate CYP2D6 inhibitors concomitantly with strong or moderate CYP3A inhibitors	Not indicated	Contraindicated	Contraindicated	N/A
Strong CYP2D6 inhibitors	Not indicated	84 mg once daily	84 mg once daily	N/A
Moderate CYP2D6 inhibitors	Not indicated	84 mg once daily	84 mg once daily	N/A
Strong CYP3A4 inhibitors	Not indicated	84 mg once daily	Contraindicated	Contraindicated
Moderate CYP3A inhibitors	Not indicated	84 mg once daily	Not recommended	Not recommended
Weak CYP3A inhibitors	Not indicated	N/A	N/A	Not recommended

Cross References
Site of Care Review, Medication Policy Manual, Policy No. dru408
Enzyme Replacement Therapies, Medication Policy Manual, Policy No. dru426

Codes	Number	Description
HCPCS	J3385	Injection, velaglucerase alfa (VPRIV), 100 units
HCPCS	J1786	Injection, imiglucerase (Cerezyme), 10 units
HCPCS	J3060	Injection, taliglucerase alfa (Elelyso), 10 units

Appendix 1: Adults with Type 1 Gaucher Disease: Risk Assessment and Dosage Recommendations [6]

Initial Dose	Highest Risk: 60 units/kg every 2 weeks	Lowest Risk: 30 units/kg or less every 2 weeks
Risk Criteria	At least one or more of the following: - **Symptomatic skeletal disease:** * Moderate to severe osteopenia defined as reduced bone mineral density (BMD) of > 1 S.D. below the mean (which predicts a relative fracture risk of 2.5 using the World Health Organization criteria). * Chronic bone pain * Bone crises * Avascular necrosis * Pathological fractures * Joint replacement(s) - **Cardiopulmonary disease, including pulmonary hypertension** - **Hematologic symptoms** * Platelet count ≤ 60,000 mm^3 or documented abnormal bleeding episodes * Symptomatic anemia or hemoglobin ≤ 8.0 g/dL * Transfusion dependency - **Significant liver disease** * Severe hepatomegaly defined as liver volume ≥ to 2.5 x norm * Infarcts * Portal hypertension * Hepatitis - **Significant splenic disease** * Severe splenomegaly defined as spleen volume > 15 x normal * Infarcts * Significant renal disease such as evidence of bilaterally reduced (< 8.5 cm) kidney size by imaging studies	- Normal liver, cardiac, lung, and renal function - Skeletal disease limited to mild osteopenia (low bone density) and Erlenmeyer flask deformity - Hemoglobin as follows: **Males: ≤** 12.5 g/dL and > 11.5 g/dL; **Females: ≤** 11.5 g/dL and > 10.5 g/dL; or overall < 2.0 g/dL below lower limit of normal for age and sex - Platelet count ≤ 120,000 per mm^3 and > 60,000 mm^3 on three determinations - Liver volume < 2.5 x normal - Spleen volume < 15 x normal

Appendix 2: Children (less than 18 years) with Type 1 Gaucher Disease: Risk Assessment and Dosage Recommendations [6]

Initial Dose	Highest Risk: 60 units/kg every 2 weeks	Lowest Risk: < 60 units/kg every 2 weeks
Risk Criteria	One or more of the following in addition to physical signs: - Symptomatic disease (manifestations of abdominal/bone pain, fatigue, exertional limitations, weakness, cachexia) - Growth failure - Evidence of skeletal involvement including Erlenmeyer flask deformity - Platelet count < 60,000 mm3 and/or documented abnormal bleeding episode(s) - Hemoglobin < 2.0 g/dL below lower limit of normal for age and sex - Impaired quality of life	Children with relevant physical signs without additional criteria described for highest risk patients.

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Revision History

Revision Date	Revision Summary
6/20/2024	• Added Elelyso (taliglucerase alfa) back into site of care program. • Updated cross references. No change to intent with update.
12/7/2023	Added Yargesa, a new generic form of miglustat to policy. No changes to criteria.
6/15/2023	No criteria changes with this annual update.
12/9/2022	Removed Elelyso (taliglucerase alfa) from site of care requirements (effective 1/15/2023).
6/17/2022	Updated reauthorization language to include current/recent clinical documentation.
7/16/2021	• Updated continuation of therapy (COT) language, as well as criteria for dose escalation, such that it applies to COT. • Clarified criteria for Niemann Pick Type C.
10/28/2020	Added back in quantity limit language to continued authorization section for Cerezyme (imiglucerase), VPRIV (velaglucerase alfa), and Elelyso (taliglucerase alfa). This was mistakenly left out when combining policies. No change to intent of criteria.
7/22/2020	New combination policy (effective 10/1/2020). Replaces individual drug coverage policies for Gaucher Disease (dru002, dru109, and dru370).

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Medication Policy Manual

Policy No: dru652

Topic: Monjuvi, tafasitamab-cxix

Date of Origin: April 1, 2021

Committee Approval Date: March 6, 2025

Next Review Date: 2026

Effective Date: May 1, 2025

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Monjuvi (tafasitamab-cxix) is a monoclonal antibody that binds to the CD19 antigen on B-lymphocytes and on several B-cell cancers, including diffuse large B-cell lymphoma (DLBCL), which ultimately causes cell death. It is given via intravenous infusion and is indicated for patients with relapsed or refractory DLBCL who are not eligible for an autologous stem cell transplant (SCT). Monjuvi (tafasitamab-cxix) is given in combination with oral Revlimid (lenalidomide).

Policy/Criteria

Most contracts require pre-authorization approval of Monjuvi (tafasitamab-cxix) prior to coverage.

I. Continuation of therapy (COT): Monjuvi (tafasitamab-cxix) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Monjuvi (tafasitamab-cxix) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A through E below are met.

A. A diagnosis of **relapsed and/or refractory diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS)** [see *Appendix 1*].

AND

B. There has been disease progression on or after at least one prior anti-CD20-based regimen (e.g., rituximab).

AND

C. The patient is not a candidate for an autologous stem cell transplant (SCT).

AND

D. Monjuvi (tafasitamab-cxix) will be initiated in combination with Revlimid (lenalidomide).

AND

E. There has been no prior use of Monjuvi (tafasitamab-cxix) or Revlimid (lenalidomide).

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Monjuvi (tafasitamab-cxix) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Monjuvi (tafasitamab-cxix) will be authorized in doses up to 12 mg/kg in quantities not to exceed the following number of infusions per 28-day cycle: five infusions in cycle 1, four infusions each in cycles 2 and 3, then two infusions per cycle thereafter, until disease progression.

C. Authorization **may** be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

IV. Monjuvi (tafasitamab-cxix) is considered investigational when used for all other conditions.

Position Statement

Summary

- Monjuvi (tafasitamab-cxix) is an intravenously administered monoclonal antibody directed against the CD19 antigen on B-lymphocytes which is present on some B-cell malignancies, including diffuse large B-cell lymphoma (DLBCL). In binding to these cells, Monjuvi (tafasitamab-cxix) ultimately causes cell death.
- Monjuvi (tafasitamab-cxix) is indicated in combination with Revlimid (lenalidomide) for the treatment of relapsed or refractory DLBCL, not otherwise specified (NOS) for patients who are not a candidate for an autologous stem cell transplant (SCT) and whose disease has progressed after at least one prior anti-CD20-based (e.g., rituximab) regimen.
- The intent of this policy is to allow coverage of Monjuvi (tafasitamab-cxix) for relapsed and refractory DLBCL NOS after progression of disease on standard front-line therapy with a rituximab-based chemotherapy regimen when patients are not eligible for an autologous stem cell transplant as detailed in the coverage criteria.
- The efficacy of Monjuvi (tafasitamab-cxix) in DLBCL is based on a low quality, open-label, single-arm, observational study the evaluated overall response rate (ORR) the primary endpoint. ORR is a surrogate endpoint that has <u>not</u> been shown to reliably predict clinically meaningful benefit such as improved survival or quality of life. Patients in the pivotal trial received concomitant Revlimid (lenalidomide) for up to 12 cycles.

- It is not known how Monjuvi (tafasitamab-cxix) compares with any other salvage DLBCL therapy.
- The most commonly reported serious adverse effects (AEs) with Monjuvi (tafasitamab-cxix) plus Revlimid (lenalidomide) included neutropenia, thrombocytopenia, anemia, pneumonia, low serum potassium, and pulmonary embolism. Approximately one in four patients stopped either one or both drugs due to an AE.
- The National Comprehensive Cancer Network (NCCN) B-cell lymphoma guideline lists Monjuvi (tafasitamab-cxix) plus Revlimid (lenalidomide) among several salvage therapy options for DLBCL NOS.
- Monjuvi (tafasitamab-cxix) is administered intravenously in a dose of 12 mg/kg on a 28-day cycle. It is given at least weekly in the first three cycles, and then every two weeks thereafter, starting with cycle 4. It is given until disease progression. Concomitant Revlimid (lenalidomide) is given daily for a maximum of 12 cycles.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy

The efficacy of Monjuvi (tafasitamab-cxix) is based on a low quality, open-label (non-blinded), single-arm (no comparator) trial that evaluated tumor response as a surrogate endpoint in patients with relapsed or refractory DLBCL NOS. [1,2] This was an FDA accelerated approval meaning that clinical benefit has not been confirmed.

- Patients enrolled in the study had a confirmed diagnosis of DBLCL NOS. This included a subset of patients that had transformed indolent lymphoma with a subsequent DLBCL relapse.

- All patients had a disease that had relapsed after, or were refractory to at least one, but no more than three systemic regimes for their DLBCL. At least one prior therapy must have included an anti-CD20-based (e.g., rituximab) chemotherapy regimen.
- Additionally, patients were not candidates for high-dose chemotherapy with a subsequent autologous stem cell transplant (SCT) based on age, other comorbidities, or inability to successfully collect peripheral blood stem cells.
- There was a 55% overall response rate (partial response plus complete remissions). The complete remission rate was 37% based on the FDA analysis of the data set (the manufacturer analysis reported higher rates).
- Neither of these medications has been shown to improve any clinically important outcome in DLBCL when used alone. A well-conducted randomized controlled trial is needed to establish whether the combination of Monjuvi (tafasitamab-cxix) and Revlimid (lenalidomide) is superior at improving clinical outcomes relative to other therapies or either agent alone.

Guidelines [3]

- The NCCN B-cell lymphoma guideline lists Monjuvi (tafasitamab-cxix) plus Revlimid (lenalidomide) among several category 2A salvage regimens for DLBCL. This recommendation applies to patients who are not candidates for transplant.

Investigational Uses

- There is no published evidence for Monjuvi (tafasitamab-cxix) outside of the relapsed or refractory DLBCL treatment setting.
- The clinicaltrials.gov database lists several planned or ongoing studies that will evaluate Monjuvi (tafasitamab-cxix) in combination with medications other than Revlimid (lenalidomide); [4] however, there is currently no information that establishes the safety or efficacy of these combinations.

Safety [2,5]

- The most commonly reported treatment-emergent adverse effects (AEs) in the pivotal Monjuvi (tafasitamab-cxix) trial included bone marrow suppression (neutropenia, anemia, and thrombocytopenia), pneumonia, hypokalemia, and pulmonary embolism.
- Deaths due to an AE occurred in 4.9% of the study population within 60 days of the last dose of Monjuvi (tafasitamab-cxix).
- Discontinuation of study drug (either drug alone, or both) occurred in about one in four patients in the trial and 70% or patients required dose modifications (either drug alone, or both) suggesting tolerability issues with this regimen in a fair number of patients.

Dosing [5]

- Monjuvi (tafasitamab-cxix) is given intravenously at a dose of 12 mg/kg in 28-day cycles on the following schedule:
    * Cycle 1: Days 1, 4, 8, 15, and 22
    * Cycles 2 & 3: Days 1, 8, 15, and 22
    * Cycle 4 and beyond: Days 1 and 15

- Revlimid (lenalidomide) is initiated with Monjuvi (tafasitamab-cxix) on the following schedule:
    * 25 mg (one capsule) orally daily on Days 1 through 21 of each 28-day cycle for a maximum of 12 cycles.

Appendix 1: DLBCL, not otherwise specified (NOS)
• Defined in the World Health Organization (WHO) classification of mature lymphoid neoplasms • Diagnosis of exclusion • ICD10 codes(s): C83.30 to C83.39, depending on site of tumor

Cross References
Bispecific T-cell Engager (BiTE) Therapies for B-cell Lymphoma, Medication Policy Manual, Policy No. dru761
Chimeric Antigen Receptor (CAR) T-cell Therapies, Medication Policy Manual, Policy No. dru523
Products with Therapeutically Equivalent Biosimilars/Reference Products, Medication Policy Manual, Policy No. dru620
Polivy, polatuzumab vedotin-piiq, Medication Policy Manual, Policy No. dru600
Xpovio, selinexor, Medication Policy Manual, Policy No. dru607
Zynlonta, loncastuximab tesirine, Medication Policy Manual, Policy No. dru675

Codes	**Number**	**Description**
HCPCS	J9349	Injection, tafasitamab-cxix (Monjuvi), 2 mg

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Revision History

Revision Date	Revision Summary
3/6/2025	No changes to coverage criteria with this annual review.
3/21/2024	No criteria changes with this annual review.
3/16/2023	No changes to coverage criteria with this annual update.
3/18/2022	• No changes to coverage criteria with this annual update • Policy language updated so standard template language (no change to intent).
1/20/2021	New policy. Limits coverage of Monjuvi (tafasitamab-cxix) to patients with relapsed or refractory DLBCL NOS when used in combination with lenalidomide in patients who are not candidates for a stem cell transplant (SCT) and whose disease has progressed after at least one prior anti-CD20-based regimen. Patients who have had progression of disease on Monjuvi (tafasitamab-cxix) and/or Revlimid (lenalidomide) are not eligible for coverage as retreatment has not been shown to be effective.

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Medication Policy Manual **Policy No:** dru657

Topic: Uplizna, inebilizumab-cdon **Date of Origin:** January 1, 2021

Committee Approval Date: September 14, 2023 **Next Review Date:** 2024

Effective Date: December 1, 2023

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Uplizna (inebilizumab-cdon) is an intravenous medication (monoclonal antibody) for neuromyelitis optica spectrum disorder (NMOSD), a rare inflammatory condition.

Policy/Criteria

Most contracts require pre-authorization approval of Uplizna (inebilizumab-cdon) prior to coverage.

I. Continuation of therapy (COT): Uplizna (inebilizumab-cdon) may be considered medically necessary for COT when criteria A, B, or C, **AND** D **AND** E below are met:

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

AND

D. Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, Site of Care Review, dru408].

AND

E. "Administration, Quantity Limitations, and Authorization Period" below applies, as well as "Investigational Uses" for combination therapy.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Uplizna (inebilizumab-cdon) may be considered medically necessary when clinical documentation (including, but not limited to chart notes), that criteria A through D below are met.

A. Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, Site of Care Review, dru408].

AND

B. A diagnosis of neuromyelitis optica spectrum disorder (NMOSD) has been established by or in consultation with a neurologist.

AND

C. Documentation of a positive serologic test for aquaporin-4 immunoglobulin (AQP4-IgG) antibodies.

AND

D. Rituximab has been ineffective as documented by symptom relapse after completion of induction (at least one month after the first dose of rituximab) or not tolerated, unless there is a documented medical contraindication to use.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Uplizna (inebilizumab) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Uplizna (inebilizumab-cdon) will be authorized in quantities as follows:

Authorization Period	**Quantity Limit**
Initial Authorization	A maximum of 9 vials (100 mg/vial) in a 48-week period based on 300 mg on week 0, 2, then 300 mg every 24 weeks (starting 24 weeks from the first infusion).
Continued Authorization	A maximum of 6 vials (100 mg/vial) per 48 weeks, based on a max dose of 300 mg every 24 weeks.

C. Authorization shall be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit including disease stability or improvement, relative to baseline symptoms. Specifically, there must be a reduction of clinical relapse OR provider attestation has been received that the patient is continuing to have clinical benefit (stability or improvement) and clinical therapy is medically necessary.

IV. Investigational Uses:

A. Uplizna (inebilizumab-cdon) is considered investigational when used for all other conditions.

B. The use of Uplizna (inebilizumab-cdon) in combination with other targeted therapies for NMOSD, including, but not limited to, anti-CD20 therapy [rituximab product], anti-CD19 therapy [Enspryng (satralizumab-mwge)], anti-IL6 therapy [Actemra (tocilizumab)], or complement inhibitors [such as Soliris (eculizumab).

C. The use Uplizna (inebilizumab-cdon) in doses/ frequencies exceeding limits in the FDA-approved prescribing information.

Position Statement

Summary

- Uplizna (inebilizumab-cdon) is a monoclonal antibody that binds to CD19. [1]
- The intent of the policy is to allow for coverage of Uplizna (inebilizumab-cdon) for the specific diagnosis for which it has been studied (as outlined in the coverage criteria), when managed by a specialist, encourage the use of lower cost therapy (when appropriate), and limit coverage to doses studied and shown to be safe and effective in clinical trials.
- Uplizna (inebilizumab-cdon) has been studied for use in neuromyelitis optica spectrum disorder (NMOSD), also known as Devic disease or neuromyelitis optica (NMO). It is a chronic demyelinating disease of the central nervous system dominated by inflammation of the optic nerve and spinal cord and may often be misdiagnosed as multiple sclerosis (MS). [2-5]
    * Stepwise deterioration due to disease relapse/attack causes an accumulation of disability. Hallmark features of NMOSD include acute nerve inflammation that leads to severe visual loss, limb weakness, sensory loss, pain, paralysis, bladder dysfunction, and intractable nausea/vomiting and hiccups.
    * Patients with NMOSD are treated for acute episodes/ relapse with steroids. Plasma exchange (plasmapheresis, PLEX) is used acutely for incomplete response to steroids.
    * Immunosuppressive therapy (IST; corticosteroids, azathioprine, mycophenolate mofetil, or rituximab) is therapy to reduce the frequency of relapse (maintenance therapy).
- Not all patients with NMOSD test positive for AQP4-IgG. Only a small percentage of patients in the clinical trial of Uplizna (inebilizumab-cdon) in NMOSD were AQP4-IgG negative (n=17, 7%). Due to the small sample size, the efficacy and safety in AQP4 seronegative patients is unknown.
- There is limited clinical experience for the use of Uplizna (inebilizumab-cdon) and the long-term safety and efficacy is unknown.

- Uplizna (inebilizumab-cdon) has not been directly compared to any other IST for NMOSD. However, use of rituximab for NMOSD is supported by clinical evidence for reducing relapse rate [including a single randomized controlled trial (RCT)[6]], is recommended by guidelines, and has years of experience in clinical practice. [2,5,7-9] Therefore, Uplizna (inebilizumab-cdon) is coverable only when rituximab is ineffective or not a treatment option.
- The evidence for Uplizna (inebilizumab-cdon) in NMOSD is limited to a single phase 3 trial. Although Uplizna (inebilizumab-cdon) reduced the frequency of NMOSD relapse compared to placebo, its effect on quality of life (QoL) and disability are unknown.
- The safety and efficacy of Uplizna (inebilizumab-cdon) in combination with other targeted therapies for NMOSD, including rituximab, Soliris (eculizumab), and Enspryng (satralizumab-mwge) have not been established. Uplizna (inebilizumab-cdon) may be covered for up to 300 mg on days 0 and 14 (initial) and every six months thereafter starting 6 months from the first infusion (maintenance), the dose studied in clinical trials. The safety and effectiveness of higher doses have not been established.
- The safety and effectiveness of Uplizna (inebilizumab-cdon) in conditions other than NMOSD have not been established.

Clinical Efficacy[10-12]

- The evidence for Uplizna (inebilizumab-cdon) in NMOSD is limited to one phase 2/3, time-to-event trial that showed that Uplizna (inebilizumab-cdon) reduced the frequency of first adjudicated relapsed compared to placebo (N-Momentum)[13].
    * Uplizna (inebilizumab-cdon) monotherapy was compared to placebo.
    * Patients enrolled in the trial had at least one relapse within the year prior to screening or at least two relapses within the two years prior to screening and had a median Expanded Disability Status Scale (EDSS) of 4.
    * The primary endpoint of first adjudicated relapse occurred in 11% in the Uplizna (inebilizumab-cdon) arm versus 42% of the placebo arm, HR 0.23 [95% CI 0.12 to 0.42].
    * The sample size of patients who were aquaporin 4 (AQP4) seronegative (n=17) was too small to determine efficacy in AQP4 seronegative patients. In AQP4 seronegative patients, three of the 13 patients who received Uplizna (inebilizumab-cdon) had a relapse versus none of the four in the placebo arm.
- Guidelines recommend treatment of acute episodes/ relapse and use of maintenance immunosuppressive therapy (IST), to reduce the frequency of relapse. [2,5,8,9,14]
    * Treatment of Relapse: Patients are usually treated with 1 g of intravenous (IV) methylprednisolone (IVMP) for 3–5 days. Relapses that do not respond to IV steroids may benefit from five to seven plasma exchange (PLEX) procedures over a 2-week period. Oral prednisone (1 mg/kg) for 1–6 months can be initiated after IVMP or PLEX to ensure a prolonged effect on inflammation until steroid sparing immunosuppressants take effect.
    * Maintenance Therapy: A variety of immunosuppressive therapy (IST) are regarded by many clinicians as first-line therapy based on primarily observational or single-arm data. The most widely prescribed treatments include:

corticosteroids, azathioprine, mycophenolate mofetil, and rituximab. The use of azathioprine and mycophenolate mofetil has fallen out of favor due to lack of efficacy and side effect profile. However, if given, they are often prescribed with low doses of corticosteroids. Rituximab has evidence for reduction of relapse rates and disability in neuromyelitis optica, based on one RCT (n=68)[6] and dozens of case series, including in patients who fail oral immunosuppressive treatments. [7-9,15-19] Paradoxical relapses may occur shortly after initiation of rituximab therapy so it is important to allow enough time for the rituximab to become effective. Complete suppression of CD20+B lymphocytes takes one month. [17]

Investigational Uses

- There are no published clinical trials evaluating the safety or efficacy of Uplizna (inebilizumab-cdon) for the treatment of other conditions not covered in this policy, or in combination with other targeted therapies for NMOSD, including, but not limited to, anti-CD20 therapy [rituximab product], anti-CD19 therapy [Enspryng (satralizumab-mwge)], anti-IL6 therapy [Actemra (tocilizumab)], or complement inhibitors [Soliris (eculizumab)].
- The safety and efficacy of Uplizna (inebilizumab-cdon) in doses exceeding FDA-label have not been studied in clinical trials.

Safety

- There is no reliable evidence to conclude that Uplizna (inebilizumab-cdon) is safer than alternatives used in NMOSD, including rituximab products.
- The recommended dose of Uplizna (inebilizumab-cdon) is 3000 mg at day 0 and 14, followed by 300 mg every 6 months as maintenance. The safety and effectiveness of higher doses have not been established.
- Uplizna (inebilizumab-cdon) is not considered a self-injectable medication for safety reasons; therefore, it is only coverable under the medical benefit. Medical observation for hypersensitivity reactions is necessary following Uplizna (inebilizumab-cdon) administration.

Cross References
Complement Inhibitors, Medication Policy Manual, Policy No. dru385
Products with Therapeutically Equivalent Biosimilars/Reference Products, Medication Policy Manual, Policy No. dru620
Enspryng, satralizumab-mwge, Medication Policy Manual, Policy No. dru656
Site of Care Review, Medication Policy Manual, Policy No. dru408

Codes	**Number**	**Description**
HCPCS	J1823	Injection, inebilizumab-cdon (Uplizna), 1 mg

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Revision History

Revision Date	Revision Summary
9/14/2023	No criteria changes with this annual review.
9/23/2022	Doses/frequencies exceeding FDA limits are considered investigational.
7/16/2021	Continuation of therapy (COT) updated. Clarified use in combination with other targeted therapies is "Investigational."
10/28/2020	New policy (effective 1/1/2021). Limits coverage to patients with NMOSD that is AQP4 seropositive (the setting in which it was studied and has a labeled indication) if rituximab products, which are standard of care with years of experience in clinical practice, are ineffective not tolerated or contraindicated.

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Medication Policy Manual | **Policy No:** dru658

Topic: Zepzelca, lurbinectedin | **Date of Origin:** November 15, 2020

Committee Approval Date: December 7, 2023 | **Next Review Date:** 2024

Effective Date: March 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Zepzelca (lurbinectedin) is an intravenous (IV) medication use for the treatment of metastatic small cell lung cancer (SCLC). It is used for patients with disease despite use of previous therapies.

Policy/Criteria

Most contracts require pre-authorization approval of Zepzelca (lurbinectedin) prior to coverage.

I. Continuation of therapy (COT): Zepzelca (lurbinectedin) may be considered medically necessary for COT when criterion A, B, or C below is met:

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 below must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 below must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Zepzelca (lurbinectedin) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) confirming that criteria A through C below are met.

A. A diagnosis of **metastatic small cell lung cancer** (SCLC).

AND

B. There has been disease progression on or after a cisplatin- or carboplatin-containing regimen.

AND

C. Zepzelca (lurbinectedin) will be used as a monotherapy.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Zepzelca (lurbinectedin) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Zepzelca (lurbinectedin) may be authorized in quantities of up to 3.2 mg/m^2 IV every 21 days until disease progression.

C. Authorization may be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

IV. Zepzelca (lurbinectedin) is considered investigational when used for all other conditions.

Position Statement

Summary

- The intent of this policy is to allow coverage of Zepzelca (lurbinectedin) in the clinical setting described above (in the coverage criteria), where it has been evaluated for efficacy, up to the dose shown to be safe in clinical trials.
- Zepzelca (lurbinectedin) is indicated for metastatic small cell lung cancer as a single agent after progression of disease on or after platinum-based chemotherapy.
- Efficacy was based on a small, single-arm trial (poor quality evidence) that evaluated tumor response as an endpoint. Zepzelca (lurbinectedin) was administered as monotherapy.
    * Approval in this setting is conditional (FDA Accelerated approval). Additional studies are needed to establish clinical benefit Indications. [1]
- The NCCN small cell lung cancer guideline lists Zepzelca (lurbinectedin) as a category 2A recommendation for subsequent treatment of metastatic SCLC along with many other chemotherapy regimens. [2]
- Zepzelca (lurbinectedin) may be covered for up to 3.2 mg/m^2 every 21 days, the dose studied in clinical trials. The safety and effectiveness of higher doses have not been established. [1]
- The safety and effectiveness of Zepzelca (lurbinectedin) in conditions other than metastatic small cell lung cancer have not been established. Zepzelca (lurbinectedin) is currently being evaluated for multiple other solid tumors, however the evidence is preliminary.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be

used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.

- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy [3]

- The evidence for Zepzelca (lurbinectedin) is based on a single, open-label, single-arm trial in patients with SCLC who had disease progression on or after platinum-based chemotherapy. Based on the poor quality of the evidence, Zepzelca (lurbinectedin) was approved via the FDA Accelerated approval pathway. Confirmatory trials are needed to establish that there is clinical benefit with this therapy.
- Zepzelca (lurbinectedin) was given as monotherapy until disease progression or unacceptable toxicity.
- Tumor response was evaluated as the primary endpoint; however, tumor response in not a validated surrogate for any clinically relevant endpoint in SCLC.
- A phase 3, randomized controlled trial (RCT) [ATLANTIS study] that was intended to be the confirmatory trial for the Accelerated approval of Zepzelca (lurbinectedin) recently failed to achieve its prespecified overall survival endpoint. [4] The manufacturer plans to perform an additional confirmatory trial using a new dosage regimen after discussions with the FDA.

Investigational Uses [5]

- Although Zepzelca (lurbinectedin) is being studied for the treatment of other types of solid tumors, there is currently no published evidence supporting its safety or efficacy in these Clinicaltrials.gov.

References

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Revision History

Revision Date	Revision Summary
12/7/2023	No criteria changes with this annual review.
12/9/2022	• Updated standard language in policy. • No changes to coverage criteria with this annual update.
1/20/2021	Updated continuation of therapy (COT) language. No changes to coverage criteria.
10/28/2020	New policy (effective 11/15/2020). Limits coverage to patients with metastatic small cell lung cancer with disease progression on or after platinum-based chemotherapy (disease), the setting in which it was studied and has a labeled indication.

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Medication Policy Manual

Policy No: dru661

Topic: Amondys 45, casimersen

Date of Origin: February 15, 2021

Committee Approval Date: June 20, 2024

Next Review Date: 2024

Effective Date: October 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Amondys 45 (casimersen) is an intravenous medication that may be used for Duchenne muscular dystrophy (DMD) when patients have a specific gene mutation. A clinical benefit, such as improved ambulation, of Amondys 45 (casimersen) has not been established.

Policy/Criteria

Most contracts require pre-authorization approval of Amondys 45 (casimersen) prior to coverage.

I. Continuation of therapy (COT): Amondys 45 (casimersen) is considered investigational for all conditions, per the full policy criteria below.

Please note: *Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Amondys 45 (casimersen) is considered investigational for all conditions, including Duchenne muscular dystrophy (DMD) that is amenable to exon 45 skipping (*Table 1*). However, if found to be medically necessary, criteria A must also be met:

A. Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, Site of Care Review, dru408].

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Amondys 45 (casimersen) coverable under the medical benefit (as a provider administered medication).

B. Although the use of Amondys 45 (casimersen) is considered investigational for all conditions, including Duchenne muscular dystrophy (DMD) that is amenable to exon 45 skipping, if pre-authorization is approved, Amondys 45 (casimersen) will be authorized in doses up to 30 mg/kg every week. (52 infusions per year).

C. Authorization shall be reviewed at least every twelve months for documented benefit. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met. Specifically, documentation that the medication is providing clinical benefit, including disease stability or improvement, and lack of disease progression.

Position Statement

Summary

- Amondys 45 (casimersen) is an intravenous therapy under FDA review for the treatment of Duchenne muscular dystrophy (DMD) when there is a confirmed mutation of the DMD gene that is amenable to exon 45 skipping. It is under evaluation through the FDA Accelerated Approval Program based on an increase in dystrophin in skeletal muscles observed in some patients during a phase III trial.
- A clinical benefit (e.g. prolongation of independent ambulation, improved quality of life, or prevention of disease progression and disability) of Amondys 45 (casimersen) has not been established.

    * In one ongoing trial, Amondys 45 (casimersen) was shown to increase dystrophin levels. However, it has not been proven that an increase in dystrophin will translate to improved clinical outcomes, such as improved motor function.

- The U.S. Centers for Disease Control and Prevention (CDC) has developed general management guidelines for DMD. The CDC recommends corticosteroids and supportive care to slow disease progression. These guidelines were published prior to the submission of Amondys 45 (casimersen) to the FDA, thus the use of Amondys 45 (casimersen) for DMD has not yet been addressed. [1-3]

Clinical Efficacy [4]

- Evidence regarding the effect of casimersen on dystrophin levels is inconclusive. Data is limited to the small, unpublished, two-part, double-blind, placebo-controlled phase III ESSENCE trial, which is ongoing. Additional trial data is needed to establish the safety and efficacy of casimersen in Duchenne muscular dystrophy (DMD).
- The primary endpoint of the ESSENCE trial is the change from baseline in the total distance walked during the 6-minute walk test (6MWT) at week 96. Change in dystrophin protein levels, change in forced vital capacity percent (FVC%), and muscular function tests (such as the ability to rise independently, time to loss of ambulation, and the North Star Ambulatory Assessment (NSAA), at week 96, were key secondary endpoints.
- In the ESSENCE trial, 43 patients were initially randomized to receive either placebo (n=17) or casimersen 30 mg/kg (n=27) via intravenous route weekly for 96 weeks. However, available data is limited to week 48. At week 48, mean dystrophin levels increased to 1.736% of normal in the casimersen 30 mg/kg group. In the casimersen treated group, the baseline dystrophin level was 0.925% of normal, therefore the absolute change in dystrophin was 0.81%. As previously mentioned, the ESSENCE trial is ongoing, and the results of all other endpoints, including the primary endpoint, have not been reported.
    * Dystrophin production is a surrogate biomarker of disease improvement with an unknown correlation to health outcomes.
    * An absolute increase in dystrophin levels has not been correlated to improved ambulation or muscle function and a minimal clinically important difference in dystrophin levels has not yet been established. Experts have proposed that dystrophin levels greater than or equal to 10% of normal may be clinically meaningful; however, validation is needed
- Lack of available trial data makes it impossible to demonstrate any meaningful conclusions regarding endpoints with functional outcomes, including 6MWT and pulmonary function resulting from casimersen treatment. Long-term comparative evidence is needed to further clarify the role of casimersen.
- Casimersen has not yet been shown to improve any clinical outcomes such as quality of life, prolongation of independent ambulation, or prevention of disease progression and disability.

Safety [4]

- Limited safety data is available, however, the most common adverse reactions reported with casimersen during phase I/II trials included procedural pain and nasopharyngitis. Safety data for the phase III trial has not been published.

Table 1: Mutations Amenable to Exon 45 skipping			
7-44	46-78	46-49	46-48
12-44	18-44	46-59	46-57
44	46	46-47	46-75
46-51	46-53	46-55	
46-60	46-67	46-69	

Cross References
BlueCross BlueShield Association Medical Policy, 5.01.27 - Treatment for Duchenne Muscular Dystrophy [June 2023]
BlueCross BlueShield Association Medical Policy, Gene Therapies for Duchenne Muscular Dystrophy [October 2023]
Exondys 51, eteplirsen, Medication Policy Manual, Policy No. dru480
Vyondys 53, golodirsen, Medication Policy Manual, Policy No. dru606
Viltepso, viltolarsen, Medication Policy Manual, Policy No. dru640
Elevidys, delandistrogene moxeparvovec, Medication Policy Manual, Policy No. dru754
Site of Care Review, Medication Policy Manual, Policy No. dru408

Codes	**Number**	**Description**
HCPCS	J1426	Injection, casimersen (Amondys 45), 10 mg
ICD-10	G71.0	Muscular dystrophy

References

1. Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. *The Lancet Neurology*. 2018;17(3):251-67. PMID: 29395989
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3. Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 3: primary care, emergency management, psychosocial care, and transitions of care across the lifespan. *The Lancet Neurology*. 2018;17(5):445-55. PMID: 29398641
4. Wagner K, Kuntz N, Koenig E, et al. Casimersen Treatment in Patients With Duchenne Muscular Dystrophy: Safety, Tolerability, and Pharmacokinetics Over 144 Weeks of Treatment. World Muscle Society Virtual Congress: Sarepta, 2020.

Revision History

Revision Date	Revision Summary
6/20/2024	Added Amondys 45 to site of care (SOC) program (effective 10/1/2024).
12/7/2023	• Added quantity limit and reauthorization criteria (no change to intent) • Updated cross references.
12/9/2022	No updates with this annual review.
1/20/2021	New policy. Effective 2/15/2021. Use of casimersen is considered investigational in the treatment of all conditions, including Duchenne muscular dystrophy (DMD) that is amenable to exon 45 skipping. The available clinical trial data was insufficient to demonstrate safety or efficacy of casimersen in the treatment of DMD.

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Medication Policy Manual | **Policy No:** dru662

Topic: Margenza, margetuximab-cmkb | **Date of Origin:** May 15, 2021

Committee Approval Date: June 20, 2024 | **Next Review Date:** 2025

Effective Date: September 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Margenza (margetuximab-cmkb) is an intravenously administered monoclonal antibody that blocks the human epidermal growth factor 2 (HER2) receptor. It is used in the treatment of HER2-positive breast cancer. It is similar to Herceptin (trastuzumab).

Policy/Criteria

I. Most contracts require pre-authorization approval of Margenza (margetuximab-cmkb) prior to coverage.

A. New starts (treatment-naïve patients): Margenza (margetuximab-cmkb) is considered not medically necessary when used in the treatment of metastatic HER2-positive breast cancer**.**

OR

B. Continuation of therapy (COT): Margenza (margetuximab-cmkb) may be considered medically necessary for COT when there is clinical documentation (including, but not limited to chart notes) confirming that criteria 1 and 2 below are met.

1. The patient is established on this therapy AND one of the following situations applies (criterion a or b below):

a. Prior to current health plan membership AND the medication was covered by another health plan.

OR

b. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission AND there is documented clinical benefit.

AND

2. Documentation of clinical benefit is provided.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Margenza (margetuximab-cmkb) coverable only under the medical benefit (as a provider-administered medication).

B. Although the use of Margenza (margetuximab-cmkb) is considered "not medically necessary," if pre-authorization is approved, Margenza (margetuximab-cmkb) will be authorized in doses up to 15 mg/kg every three weeks until disease progression.

C. Authorization **may** be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

III. Margenza (margetuximab-cmkb) is considered investigational when used for all other conditions, including but not limited to:

A. Use in combination with other HER2-directed medications (see *Appendix 1*).

B. HER2-positive gastric cancer.

Position Statement

Summary

- Similar to trastuzumab (Herceptin, biosimilars), Margenza (margetuximab-cmkb) is an intravenously administered monoclonal antibody that slows cancer growth by blocking the human epidermal growth factor receptor 2 protein (HER2).
- Margenza (margetuximab-cmkb) is approved for use in adults with metastatic HER2-positive breast cancer (BC) who have had two or more prior HER2-directed regimens, at least one of which was given in the metastatic disease setting. It is given in combination with chemotherapy.
- This policy considers the use of Margenza (margetuximab-cmkb) in patients with metastatic HER2-positive BC to be 'not medically necessary' because it has similar safety and efficacy to currently available products but is more costly. There is no evidence of superior safety or efficacy, to suggest additional health outcome benefit, such as improved overall survival (OS), for the higher cost.
- The efficacy of Margenza (margetuximab-cmkb) is similar to the efficacy of trastuzumab (Herceptin, biosimilars). In the final efficacy analysis of the pivotal trial (SOPHIA) no difference in OS between Margenza (margetuximab-cmkb) and trastuzumab was detected.
- The safety of Margenza (margetuximab-cmkb) is also similar to that of trastuzumab (Herceptin, biosimilars), including the box warning describing the potential for left ventricular dysfunction.
- The NCCN breast cancer guideline lists several HER2-directed regimens among recommended options for use in metastatic HER2-postive BC. Ideal sequencing of regimens in the second- and subsequent-line treatment settings has not been determined.
- Margenza (margetuximab-cmkb) is dosed as 15 mg/kg intravenously every 3 weeks until disease progression.
- Margenza (margetuximab-cmkb) is being evaluated in other HER2-postive tumors (e.g. gastric cancers); however, efficacy in cancers other than metastatic HER2-positive breast cancer has not been established.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit

relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.

- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy

- The available evidence for Margenza (margetuximab-cmkb) is of fair quality. The primary study (SOPHIA) compared Margenza (margetuximab-cmkb) plus investigator's choice of single-agent chemotherapy with trastuzumab plus single-agent chemotherapy in patients with metastatic HER2-positive breast cancer. [1,2]
    * All patients in the study had received prior trastuzumab and pertuzumab (Perjeta), and 91% received prior Kadcyla (ado-trastuzumab emtansine).
    * Overall, 92% of patients received at least two prior lines of therapy in the metastatic treatment setting.
- There was a 0.9-month improvement in median progression-free survival (PFS) with Margenza (margetuximab-cmkb) relative to trastuzumab. Although this difference was statistically significant, it is not likely clinically relevant. Furthermore, PFS (a surrogate endpoint) has not been shown to accurately predict improvement in clinical outcomes in breast cancer.
- Overall survival (OS) was a coprimary endpoint in this study. The final survival analysis from the pivotal trial (SOPHIA) found there was no difference in OS between Margenza (margetuximab-cmkb) and trastuzumab. [3]
- Margenza (margetuximab-cmkb) is a 'me-too' product that works via a similar mechanism as trastuzumab. It was thought that Margenza (margetuximab-cmkb) might have a theoretical advantage over trastuzumab based on increased binding activity to Fc receptor FCGR3A (CD16A); however, there is currently no clinical data to support any superiority in patients with tumors with CD16A genotypes (FF, FV, VV). Ultimately, the final OS analysis showed no difference between the two HER2-blocking antibodies.

Guidelines

- The National Comprehensive Cancer Network (NCCN) breast cancer guideline lists several HER2-directed therapies (both category 1 and 2A recommendations) among potential options for use in managing HER2-positive breast cancer. [4]
- Optimal sequencing of HER2-directed therapies in the second- and subsequent-line metastatic breast cancer setting has not been determined.

Investigational Uses

- Margenza (margetuximab-cmkb) has only been studied in combination with single-agent chemotherapy in the pretreated, metastatic breast cancer setting. There is currently no evidence evaluating its use in combination with other HER2-directed therapies. Therefore, this use is considered investigational.
- The clinicaltrials.gov database describes an ongoing trial with Margenza (margetuximab-cmkb) in HER2-positive gastric cancer. Whether there is any clinical benefit in this setting has not been adequately defined. Therefore, this use is considered investigational. [5]

Safety [6]

- The safety and warnings associated with the use of Margenza (margetuximab-cmkb) are similar to those experienced with trastuzumab.
- Similar to trastuzumab, adverse effects (AEs) requiring some sort of an intervention (Grade 3 or 4 AEs) occurred in just over half the patients who received Margenza (margetuximab-cmkb).

Dosing [6]

- Margenza (margetuximab-cmkb) is dosed as 15 mg/kg intravenously every three weeks until disease progression. It is given in combination with single-agent chemotherapy.
- Dosing of Margenza (margetuximab-cmkb) may be interrupted or permanently discontinued for decreases in left ventricular ejection fraction (LVEF). Refer to package labeling for specific parameters.

Appendix 1: HER2-Directed Medications Used in Treating HER2-Positive Breast Cancer [a]

Infused Medications (Medical Benefit)	Oral Medications (Pharmacy Benefit)
Margenza (margetuximab-cmkb)	Tykerb (lapatinib)
Perjeta (pertuzumab)	Nerlynx (neratinib)
Phesgo (pertuzumab-trastuzumab)	Tukysa (tucatinib)
trastuzumab (Herceptin, biosimilars)	
Herceptin Hylecta (trastuzumab-hyaluronidase)	
Kadcyla (ado-trastuzumab emtansine)	
Enhertu (fam-trastuzumab deruxtecan-nxki)	

[a] Currently available HER2-directed medications for BC, as of the time of this policy date. This list may be incomplete.

Cross References
Products with Therapeutically Equivalent Biosimilars/Reference Products, Medication Policy Manual, Policy No. dru620
Enhertu, fam-trastuzumab deruxtecan-nxki, Medication Policy Manual, Policy No. dru623
Kadcyla, ado-trastuzumab emtansine, Medication Policy Manual, Policy No. dru298
Nerlynx, neratinib, Medication Policy Manual, Policy No. dru520
Pertuzumab-containing medications, Medication Policy Manual, Policy No. dru281
Tukysa, tucatinib, Medication Policy Manual, Policy No. dru646
Tykerb, lapatinib, Medication Policy Manual, Policy No. dru145

Codes	Number	Description
HCPCS	J9353	Injection, margetuximab-cmkb (Margenza), 5 mg

References

1. Center for Drug Evaluation and Research; U.S. Food and Drug Administration Multi-Discipline Review BLA 761-150, margetuximab (Margenza™). [cited 1/27/2021]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/761150Orig1s000MultidisciplineR.pdf.
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5. National Institutes of Health, Clinicaltrials.gov [website]. [cited periodically]. Available from: www.clinicaltrials.gov.
6. Margenza® (margetuximab) [package insert]. MacroGenics, Inc.; Rockville, MD; May 2023.

Revision History

Revision Date	Revision Summary
6/20/2024	No changes to coverage criteria with this annual review.
6/15/2023	No changes to coverage criteria with this annual update.
6/17/2022	No criteria changes with this annual update.
4/21/2021	New policy (effective 05/15/2021). The policy considers coverage of Margenza (margetuximab-cmkb) as 'not medically necessary' because it is similar in safety and efficacy to trastuzumab but is more costly.

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Medication Policy Manual **Policy No:** dru668

Topic: Medications for Primary Hyperoxaluria **Date of Origin:** May 15, 2021

- Oxlumo, lumasiran
- Rivfloza, nedosiran

Committee Approval Date: June 20, 2024 **Next Review Date:** 2025

Effective Date: September 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Medications in this policy are used to treat primary hyperoxaluria type 1 (PH1), a rare genetic condition that can lead to kidney disease. They are given by subcutaneous (SC) injection.

Policy/Criteria

Most contracts require pre-authorization approval of Medications for Primary Hyperoxaluria (as listed in Table 1) prior to coverage.

I. Continuation of therapy (COT): Medications for Primary Hyperoxaluria (as listed in *Table 1*) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, full policy criteria must be met for coverage.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Medications for Primary Hyperoxaluria (as listed in *Table 1*) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A through D are met.

A. A diagnosis of **primary hyperoxaluria type 1** (PH1) has been established by, or in consultation with, a hepatologist, nephrologist, or urologist.

AND

B. The diagnosis of PH1 has been confirmed by genetic testing, with documentation of a mutation to the alanine-glyoxylate aminotransferase (AGT) gene.

AND

C. Confirmation of objective kidney dysfunction such as a decrease in renal function (reduced glomerular filtration rate, GFR, recurrent kidney stones [nephrolithiasis], or nephrocalcinosis).

AND

D. Medical management has been ineffective in reducing urinary oxalate levels as defined by a trial of ALL of the following (1 through 3), unless contraindicated:

1. Hydration therapy.

AND

2. Crystallization inhibitors (such as neutral phosphate, potassium citrate-citric acid, and magnesium oxide).

AND

3. Pyridoxine (vitamin B6).

PLEASE NOTE: Ineffective is defined as having a 24-hour urine oxalate excretion ≥ 0.7 mmol/24 hr/1.73 m^2 for those over 6 years of age, or urinary oxalate-to-creatinine ratio greater than the upper limit of normal for those less than 6 years of age.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Oxlumo (lumasiran) coverable only under the medical benefit (as a provider-administered medication).

B. Regence Pharmacy Services considers Rivfloza (nedosiran) coverable under the medical or pharmacy benefit (as either a provider or self-administered medication).

C. When pre-authorization is approved, Medications for Primary Hyperoxaluria may be authorized in quantities up to those listed below in *Table 1*:

Table 1: Medications for Primary Hyperoxaluria

Medication	Age	Weight	Dose
Oxlumo (lumasiran)	not age-based	Less than 10 kg	6 mg/kg subcutaneously (SC) once monthly for 3 doses, followed by 3 mg/kg SC once monthly thereafter
		10 to less than 20 kg	6 mg/kg SC once monthly for 3 doses, followed by 6 mg/kg SC every three months thereafter
		20 kg or greater	3 mg/kg SC once monthly for 3 doses, followed by 3 mg/kg SC every three months thereafter
Rivfloza (nedosiran)	12 years and older	Less than 50 kg	128 mg SC once monthly
		50 kg or greater	160 mg SC once monthly
	9 to 11 years	Less than 50 kg	3.3 mg/kg SC once monthly, not to exceed 128 mg
		50 kg or greater	160 mg SC once monthly

D. Authorization **shall** be reviewed at 6 months (initial reauthorization), then **shall** be reviewed every 12 months thereafter. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, as defined by ALL of the following:

1. A reduction in urinary oxalate excretion, kidney stone events, nephrocalcinosis, or plasma oxalate levels, as compared to baseline.

AND

2. Patient is not on dialysis.

AND

3. Patient has not had a liver transplant,

IV. Medications for Primary Hyperoxaluria are considered not medically necessary for use in patients that are currently on dialysis, or after a liver transplant.

V. Medications for Primary Hyperoxaluria are considered investigational when used for all other conditions, including primary hyperoxaluria types 2 and 3 (PH2 and PH3).

VI. The concomitant use of Medications for Primary Hyperoxaluria, such as Oxlumo (lumasiran) with Rivfloza (nedosiran), is considered investigational.

Position Statement

Summary

- Medications for Primary Hyperoxaluria are subcutaneous therapies indicated for the treatment of primary hyperoxaluria type 1 (PH1), a rare genetic condition that leads to oxalate-related renal dysfunction and may include renal failure, systemic oxalosis, and associated sequelae.
- Medications for Primary Hyperoxaluria (as listed in Table 1) are a small interfering ribonucleic acids (siRNAs) that inhibit the messenger RNA of specific enzymes hydroxyacid oxidase 1 (HAO1) and hepatic lactate dehydrogenase (LDHA), respectively], both of which are involved in the pathway that leads to excessive oxalate production. The intent of this policy is to cover Medications for Primary Hyperoxaluria (as listed in Table 1) for the indication and dose for which they have been shown to be safe and effective, for genetically confirmed, clinically significant PH1 when medical management has been ineffective in controlling urinary oxalate excretion, as detailed in the coverage criteria.
- The approval of Oxlumo (lumasiran) was based on two phase 3 trials which demonstrated a reduction in urine oxalate (Uox) excretion in patients with PH1 and relatively preserved renal function. High urinary oxalate levels at diagnosis, and upon follow-up, have been strongly correlated with worse kidney outcomes, including long-term renal survival. Subsequently, Oxlumo (lumasiran) was also studied and shown to be effective for reduction in plasma oxalate (Pox) in patients with advanced kidney disease (including those on dialysis).

- The approval of Rivfloza (nedosiran) was based on one phase 3 trial in patients with PH1 and PH2 and relatively preserved renal function. Statistically significant reductions in urinary oxalate excretion were demonstrated in the PH1 population, but not in the primary hyperoxaluria type 2 (PH2) population.
- PH1 is a heterogenous disease, with a range of phenotypes, from mildly symptomatic to severe infantile oxalosis and kidney failure. Due to the cost, Medications for Primary Hyperoxaluria are coverable only in patients with PH1 and objective evidence of clinically significant kidney disease despite use of standard of care medical management (hydration therapy, crystallization inhibitors, and pyridoxine) for reduction of urinary calcium oxalate levels.
- Liver transplant is the functional cure for PH1, as it corrects the underlying metabolic defect. Therefore, use of Medications for Primary Hyperoxaluria (as listed in Table 1) after liver transplant is considered not medically necessary.
- There is limited evidence for the use of Medications for Primary Hyperoxaluria in patients with PH1 who are on dialysis. Chronic high urinary oxalate levels can lead to end-stage kidney disease (ESKD) and need for dialysis. A renal transplant is often warranted in patients on dialysis. Based on one trial. Oxlumo (lumasiran) reduces production of oxalate but would not reverse hyperoxaluria-related renal failure. Although Medications for Primary Hyperoxaluria can be used for reduction of plasma oxalate, dialysis also clears excess plasma oxalate. The additional benefit of use of Medications for Primary Hyperoxaluria in patients already on dialysis is unknown. Therefore, the use of Medications for Primary Hyperoxaluria in patients on dialysis is considered 'not medically necessary.'

Disease background: [1-3]

- PH1 is caused by mutations in the alanine-glyoxylate aminotransferase (AGT) gene, AGXT, which results in the absence or defect in AGT. This leads to a significant increase in oxalate production by the liver.
- In the early stages of PH1, excess oxalate is excreted by the kidney. Urinary calcium oxalate supersaturation in the kidneys leads to bladder/kidney stones and nephrocalcinosis (deposits of calcium oxalate crystals in kidney parenchyma). Over time, renal inflammation, fibrosis and, if persistent, end-stage kidney disease (ESKD) occurs.
- Once a patient develops ESKD, oxalate cannot be excreted, leading to oxalate accumulation in the plasma and subsequent systemic oxalosis. Resulting non-renal complications may include cardiac arrest, poor circulation, bone pain, decreased visual acuity and hypothyroidism, among other manifestations, all of which are associated with significant morbidity and mortality.
- Medical management with the use of hydration therapy, crystallization inhibitors, and pyridoxine can effectively reduce urinary calcium oxalate levels and is considered the standard of care.
- Normal urinary oxalate excretion levels are < 0.5mmol or < 45mg per 1.73 m^2 per 24 hours.
- Liver transplant is the functional cure for PH1, as it corrects the underlying metabolic defect.

Clinical Efficacy

- Oxlumo (lumasiran)
  - The initial efficacy of Oxlumo (lumasiran) was based on interim data from two multicenter phase 3 trials, which measured reduction in urinary oxalate (Uox) excretion in patients with genetically confirmed PH1 and relatively preserved kidney function. [1 4-6]
    - ILLUMINATE-A: A multicenter, double-blind, placebo-controlled randomized controlled trial in patients ≥ 6 years and an estimated glomerular filtration rate (eGFR) of at least 30 ml/min/1.73 m^2 (n=39). [6]
      - Patients were randomized to 2:1 to lumasiran or placebo.
      - The majority of patients (82%) had an eGFR of ≥ 60 ml/min/1.73 m^2.
      - The primary endpoint was percent change in 24-hour urinary oxalate (Uox) excretion from baseline to month 6.
      - At 6 months, there was a -65.4% and -11.8% reduction change 24-hour Uox with Oxlumo (lumasiran) and placebo groups, respectively. The translates into an absolute change of -1.24 mmol/24hr/1.73m^2 and -0.27 mmol/24hr/1.73m^2, in the Oxlumo (lumasiran) and placebo groups, respectively.
    - ILLUMINATE-B: A single-arm, open-label trial in patients < 6 years of age and an eGFR of at least 45 ml/min/1.73 m^2 (or 'normal' eGFR for those < 12 months old). [5 7]
      - A total of 18 patients were enrolled, but only the first 16 were used in the primary analysis.
      - Median eGFR was 111 ml/min/1.73 m^2 (65-174).
      - The primary endpoint was percent change in spot urinary oxalate to creatinine ratio (Uox:Cr) from baseline to month 6.
      - Use of Oxlumo (lumasiran) resulted in a 71.1% reduction in spot Uox:Cr ratio at month 6 in those treated with Oxlumo (lumasiran).
      - A follow-up 12-month analysis showed sustained reduction in spot Uox:Cr at month 12. [5]

- Rivfloza (nedosiran)
  - The efficacy of Rivfloza (nedosiran) in the treatment of PH1 was based on results from a multinational, randomized, double-blind, placebo-controlled trial, PHOX2, and interim data from an ongoing phase 3 extension trial (PHYOX3). [8-10]
    - PHYOX2 enrolled 35 patients, 6 years of age and older, with PH1 or PH2, who received treatment with nedosiran or placebo, in a 2:1 randomization, respectively.
    - All subjects had relatively preserved kidney function (eGFR ≥30ml/min/1.73m^2), urinary oxalate excretion levels ≥0.7mmol/24hr/1.73m^2, the majority of subjects (>75%) had eGFR

≥60ml/min/1.73m^2 (stage 1 or 2 kidney disease), 60% were on pyridoxine, and subjects with a history of a liver or kidney transplant or on dialysis were excluded.

* PHYOX2 met its primary endpoint, demonstrating a statistically significant reduction in 24-hour urinary oxalate excretion (Uox) in subjects with PH1, from baseline to month 6.
    - At 6 months, in the PH1 population (n=29) , there was a -50% and 6% reduction change in 24-hour urinary oxalate excretion with Rivfloza (nedosiran) and placebo groups, respectively. The between group difference was a -56% reduction.
    - Despite the inclusion of a small number of subjects (n=6) with primary hyperoxaluria type 2 (PH2) in the pivotal trial (PHYOX2), there was no treatment benefit observed in this subject population. Therefore, the use of Rivfloza (nedosiran) is considered investigational given the absence of evidence, in patient populations other than primary hyperoxaluria type 1 (PH1) only.
* In PHYOX3: Reductions in 24-hour urinary oxalate excretion were maintained in the 13 patients with PH1 assigned to nedosiran treatment, over an additional 6 months.
* Secondary endpoints relating to improvements in eGFR, reduction in plasma oxalate levels, reduction in kidney stone size and occurrence were not met with statistical significance; more trials are needed to assess efficacy for these outcomes.
* Despite the causal role of urinary oxalate in kidney stone formation and kidney damage, the clinically pertinent magnitude of reduction during excretion is unknown and to what extent the reduction could predict a clinical benefit. Additional evidence is needed to establish the clinical benefit (e.g., prolongation of renal function, a decrease in kidney stone events, avoidance of systemic oxalosis complications, and a decrease in the need for liver/renal transplantation).

- Current available evidence for both available Medications for Primary Hyperoxaluria is limited to reduction in urinary oxalate, as well as plasma oxalate with Oxlumo (lumasiran) only. Additional evidence is needed to establish the clinical benefit (e.g., prolongation of renal function, a decrease in kidney stone events, avoidance of systemic oxalosis complications, and a decrease in the need for liver/renal transplantation). Evidence for any of these health outcomes is limited to very small exploratory analyses.
- Liver transplant is a functional cure for PH1. Therefore, use of Medications for Primary Hyperoxaluria after liver transplant is considered 'not medically necessary,' as the underlying metabolic issue has been reversed by the transplant.
- Dialysis can be used to clear excess oxalate; therefore, the use of Medications for Primary Hyperoxaluria in patients on dialysis is considered 'not medically necessary.' There is insufficient evidence to establish that Medications for Primary Hyperoxaluria provide additional benefit as compared to hemodialysis (HD) alone for patients on HD.

* The available evidence is limited to one single-arm, open-label phase 3 trial (ILLUMINATE-C) which evaluated Oxlumo (lumasiran) for reduction in plasma oxalate (Pox) excretion in patients with PH1 and advanced kidney disease, defined as eGFR < 45 ml/min/1.73 m^2 including patients on HD (n=21). [11]
    - The trial included two cohorts:
        - Cohort A (n=6): those not receiving hemodialysis (HD) at study enrollment. Median eGFR was 16.5 ml/min/1.73 m^2 (8.6-34.1).
        - Cohort B (n=9): those on HD at study enrollment.
    - All enrolled patients had a plasma oxalate level of ≥ 20 µmol/L at screening, including patients with or without systemic oxalosis.
    - Baseline median Pox level was 57.9 in Cohort A and 103.7 in Cohort B. Note: upper limit of normal in healthy patients is 12.11 µmol/L.
    - The primary endpoint was percent change in plasma oxalate (Pox) from baseline to month 6 for Cohort A (non-dialysis) and percent change in pre-dialysis Pox from baseline to month 6 for Cohort B (patients on dialysis).
    - At 6 months, there was a -33.3% and -42.4% reduction in Pox levels for Cohorts A and B, respectively.
    - This trial is additional evidence that Oxlumo (lumasiran) reduces plasma oxalate levels in patients with PH1. However, key health outcomes, such as improvement in renal function or reversal of other sequelae from elevated POx/Uox, remains unknown.
* Although there was a reduction in Pox in patients on hemodialysis (Cohort B), the benefit of Oxlumo (lumasiran) relative to the use of hemodialysis alone for removal of oxalate is unknown.
* Rivfloza (nedosiran) has not specifically been studied in patients on hemodialysis; however, similar to Oxlumo (lumasiran), dialysis can be used to clear excess oxalate and the superiority of use of Rivfloza (nedosiran) with dialysis versus dialysis alone is unknown.
* Therefore, the use of Medications for Primary Hyperoxaluria in patients on dialysis is considered 'not medically necessary.'

Investigational Uses

- There is the potential for off-label use of Medications for Primary Hyperoxaluria in secondary hyperoxaluria or other forms of primary hyperoxaluria, such as type 2 or 3. Medications for Primary Hyperoxaluria [Oxlumo (lumasiran) and Rivfloza (nedosiran)] have so far not been shown to be effective in these populations. Therefore, the use in any other condition is considered investigational.

Dosing and Administration [4 8]

- Oxlumo (lumasiran) is administered only by a healthcare provider.
- Rivfloza (nedosiran) may be administered by a healthcare provider or caregiver/patient,

Codes	Number	Description
		Injection, nedosiran (Rivfloza), 80 mg, 128 mg, 160 mg
HCPCS	J0224	Injection, lumasiran (Oxlumo), 0.5 mg

Cross References
BlueCross BlueShield Association Medical Policy, 5.01.37 - Lumasiran for Primary Hyperoxaluria Type 1 [August 2023]

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Revision History

Revision Date	Revision Summary
06/20/2024	No criteria changes with this annual review.
03/21/2024	• Added Rivfloza (nedosiran) to policy. • Policy name updated to Medications for Primary Hyperoxaluria
6/15/2023	No criteria changes with this annual update.
6/17/2022	No criteria changes with this annual update.
4/21/2021	New policy (effective 5/15/2021). Limits coverage to patients with genetically confirmed, clinically significant PH1, when medical management has been ineffective in controlling urinary oxalate excretion.

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Medication Policy Manual

Policy No: dru669

Topic: Cosela, trilaciclib

Date of Origin: August 15, 2021

Committee Approval Date: June 20, 2024

Next Review Date: 2025

Effective Date: September 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Cosela (trilaciclib) is an intravenous medication that is intended to protect the bone marrow in patients with small cell lung cancer (SCLC) who are receiving specific chemotherapy regimens.

Policy/Criteria

Most contracts require pre-authorization approval of Cosela (trilaciclib) prior to coverage.

I. Continuation of therapy (COT): Cosela (trilaciclib) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Cosela (trilaciclib) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A and B below are met.

A. A diagnosis of **extensive-stage small cell lung cancer** (ES-SCLC).

AND

B. The patient is being treated with a platinum/etoposide- or a topotecan-containing chemotherapy regimen.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Cosela (trilaciclib) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Cosela (trilaciclib) may be approved in doses up to 240 mg/m^2 given daily prior to each scheduled chemotherapy administration.

C. Authorization **shall** be reviewed at least every six months. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

IV. Cosela (trilaciclib) is considered investigational when used for all other conditions, and with cytotoxic chemotherapy other than what is described in the coverage criterion above.

Position Statement

Summary

- Cosela (trilaciclib) is a transient inhibitor of cyclin-dependent kinase (CDK) 4 and 6. When given prior to certain cytotoxic chemotherapy regimens, it temporarily stops the development of hematopoietic stem and progenitor cells which may protect the bone marrow from chemotherapy-induced damage.
- Based on its mechanism of action, there is the concern that Cosela (trilaciclib) might also interfere with the effectiveness of cytotoxic chemotherapy. Longer term follow-up in post-marketing studies is needed to evaluate this risk.
- Cosela (trilaciclib) is approved to decrease the incidence of chemotherapy-induced myelosuppression in adult patients when administered prior to a platinum/etoposide- or topotecan-containing regimen for extensive-stage small cell lung cancer (ES-SCLC).
- The intent of this policy is to provide coverage for Cosela (trilaciclib) in the setting in which it was studied and was subsequently approved.
- In clinical trials, Cosela (trilaciclib) decreased the duration of severe neutropenia as well as the proportion of patients experiencing severe neutropenia relative to placebo. These endpoints are surrogates for fever and neutropenia and infections, which were not measured in the trials.
- The Cosela (trilaciclib) studies did not evaluate overall survival which is necessary to give important insight into whether this therapy may interfere with the effectiveness of cytotoxic chemotherapy.
- The National Comprehensive Cancer Network (NCCN) lists Cosela (trilaciclib) as an option in the population in which it is indicated in package labeling.
- Cosela (trilaciclib) is given as an intravenous infusion just prior to each dose of cytotoxic chemotherapy in a dose of 240 mg/m^2.

- Use of Cosela (trilaciclib) with chemotherapy regimens or in conditions outside of its labeled indication has not been adequately evaluated is considered investigational.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy [1-4]

- The evidence for Cosela (trilaciclib) is based on three, small trials (GIT28-02, GIT28-03, GIT28-05) in patients with extensive-stage small cell lung cancer (ES-SCLC) who were receiving a platinum/etoposide- or topotecan-based chemotherapy regimen. These chemotherapy regimens are notable for their myelotoxicity.
- Cosela (trilaciclib) was administered as part of supportive care prior to each dose of chemotherapy.
    * The trials evaluated duration of severe neutropenia (DSN) and the proportion of patients with severe neutropenia (SN) as coprimary endpoints. DSN and SN are surrogate markers for fever and neutropenia which was not measured as an outcome in the trial.
        - The DSN was generally decreased by approximately 3.5 days in the Cosela (trilaciclib) versus the placebo arm in each of the trials.
        - The proportion of patients with SN decreased by approximately 35% in the Cosela (trilaciclib) versus the placebo arm in each of the trials.
    * An FDA supplementary analysis of the trials found that the numerical advantage for Cosela (trilaciclib) to reduce infection risk, the clinical outcome of importance,

was numerically small. Four of 122 patients (3%) and 7 of 118 patients (6%) in the Cosela (trilaciclib) and placebo groups were identified as having the severe AE of fever and neutropenia, respectively. The proportion of patients with grade 3 or higher pneumonia was identical in the two treatment arms.

* Though there was an incremental decrease in the number of patients who received filgrastim during the first treatment cycle in the trials, the majority of patients still required filgrastim as part of their supportive care.

- The National Comprehensive Cancer Network (NCCN) Small Cell Lung Cancer guideline lists Cosela (trilaciclib) as a potential supportive care option when given prior to platinum/etoposide- (with or without a checkpoint inhibitor) or topotecan-containing regimens for ES-SCLC. [5]

Investigational Uses [6]

- Use of Cosela (trilaciclib) in cancers other than ES-SCLC, or prior to cytotoxic chemotherapy other than that which is listed in package labeling is considered investigational.
- There is interest in using Cosela (trilaciclib) prior to cytotoxic chemotherapy for triple negative breast cancer (TNBC); however, benefit in this population has not been established.

Safety [1]

- Based on its mechanism of action (temporarily arrests the development of hematopoietic stem and progenitor cells), Cosela (trilaciclib) could theoretically protect tumor cells from the cytotoxic effects of chemotherapy. This potential risk was alluded to in one of the pivotal trials (GIT28-03) where a numeric difference in discontinuations due to disease progression disfavoring Cosela (trilaciclib) was observed. As a result of this finding, there is a post-marketing commitment (requiring at least two additional years of follow up) to assess its potential effects on chemotherapy efficacy.
- In the safety population the proportion of deaths related to treatment-emergent adverse effects (AEs) was numerically higher in the Cosela (trilaciclib) treatment arm than in the placebo treatment arm (5% versus 3%, respectively).

Dosing [7]

- Cosela (trilaciclib) is a prophylactic medication which is administered prior to chemotherapy on each day that chemotherapy is administered. The infusion must be completed within 4 hours prior to the start of chemotherapy.
- In patients with ES-SCLC, platinum/etoposide-based regimens are generally given on Days 1, 2, and 3 of each cycle for four total cycles. Cycles are 21 to 28 days in length. Topotecan-based regimens are typically given on Days 1 through 5 of each 21-day cycle. A course of therapy is generally 4 cycles but may range up to until there is disease progression.
- Cosela (trilaciclib) is administered intravenously over 30 minutes in a dose of 240 mg/m^2.

Codes	Number	Description
HCPCS	J1448	Injection, trilaciclib (Cosela), 1 mg

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Revision History

Revision Date	Revision Summary
6/20/2024	No criteria changes with this annual review.
9/14/2023	No criteria changes with this annual review.
9/23/2022	There were no changes to coverage criteria with this annual update.
7/16/2021	New policy (effective 8/15/2021). The policy provides coverage of Cosela (trilaciclib) in patients with ES-SCLC who are receiving platinum/etoposide- or topotecan-based chemotherapy.

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Medication Policy Manual

Policy No: dru670

Topic: Aduhelm, aducanumab

Date of Origin: August 15, 2021

Committee Approval Date: July 16, 2021

Next Review Date: January 2022

Effective Date: August 15, 2021

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Aducanumab (Aduhelm) is an intravenous medication that is used for Alzheimer's disease (AD). A clinical benefit, such as slowing of disease progression, of aducanumab (Aduhelm) has not been established.

Policy/Criteria

Most contracts require pre-authorization approval of aducanumab (Aduhelm) prior to coverage.

I. Continuation of therapy (COT): Aducanumab (Aduhelm) may be considered medically necessary for COT when full policy criteria below are met, including quantity limit.

Please note: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.

II. New starts (treatment-naïve patients): Aducanumab (Aduhelm) is considered investigational for all conditions, including Alzheimer's disease (AD).

Position Statement

Summary

- Aducanumab (Aduhelm) is an intravenous therapy indicated for the treatment of Alzheimer's disease. Aducanumab was approved via the accelerated approval pathway; continued approval may be contingent upon verification of clinical benefit in confirmatory trials.
- A clinical benefit (e.g. prolongation of independence, improved quality of life, prevention of disease progression and disability) of aducanumab (Aduhelm) has not been established.[1]
    * The results of two nearly identical unpublished studies (EMERGE and ENGAGE)[1 2] of aducanumab (Aduhelm) had inconsistent clinical benefit after 18 months of treatment. Of the two trials, one demonstrated cognitive and functional improvements based on clinical scores in a subgroup who received high-dose aducanumab while no endpoint was met in a second study regardless of dose.
    * The same studies demonstrated dose-dependent improvements in amyloid beta imaging in a subgroup population. However, the reduction of beta-amyloid plaque is a surrogate endpoint whose causal link to clinical benefit has not been established.
    * The use of aducanumab (Aduhelm) for AD is considered investigational, given the lack of overall clinical benefit and potential for harms.
- Treatment of AD is largely supportive and may include the avoidance of poly-pharmacy as well as treatment of comorbid conditions. Currently available pharmacological therapy focuses on symptom management but does not modify disease course.[3]

Clinical Efficacy

- The results of two nearly identical studies did not have consistent clinical benefit after 18 months of treatment. The FDA standard is typically 2 demonstrative clinical trials with positive data on patient reported outcomes/symptoms.
- The evidence regarding the effect of aducanumab (Aduhelm) is based on the change from baseline on the CDR-Sum of Boxes is inconclusive. The (CDR-SB) is an extensive cognitive and functional assessment tool used primarily in clinical trials. Higher scores suggest greater disease severity; a minimal clinically significant difference (MCID) is estimated to be 1-2 points.[4]
- Patients in the pivotal trials had prodromal or mild AD along with confirmed amyloid pathology [positive amyloid positron emission tomography (PET) scan]. All patients in the trials had either mild cognitive impairment associated with AD or mild AD; patients with more severe disease were not studied.
    * EMERGE: A statistically significant improvement in CDR-SB was observed in the high-dose aducanumab arm (difference vs. placebo -0.39 [95% CI -0.69 to -0.09]) but not the low-dose arm. Although the results were statistically significant in the high-dose arm, the change in CDR-SB was less than the 1-2 point change that has been suggested as the MCID.
    * ENGAGE: Neither low dose or high dose had any statistically significant improvement vs placebo in CDR-SB or any secondary efficacy endpoints.
- Both studies demonstrated significant improvements in amyloid plaques based on PET imaging; however, the effect of amyloid beta on clinical outcomes has not yet been established. There have been 16 trials of other drugs in which the treatment arm did worse than placebo despite reduction of amyloid, albeit typically in a population with more severe disease.
- Although the existing evidence is promising, an additional confirmatory trial is needed to establish the safety and efficacy of aducanumab (Aduhelm) in AD. Aducanumab has not yet proven to improve clinically relevant outcomes such as quality of life, prolongation of independent functioning, or prevention of disease progression and disability, or mortality.
- The FDA advisory committee as well as the Institute for Clinical and Economic Review (ICER) openly advised against approval of aducanumab.[5 6] Prior to approval, the American Academy of Neurology (AAN) advised against a broad label approval and that further characterization of patients who would benefit most is warranted.[3]
- At this time, there is not enough data available to determine that the benefits of aducanumab use would outweigh the risks or provide any meaningful benefit in the AD population. Aducanumab has uncertain benefit in the face of known harms.

Safety

- 40% of patients on the high-dose aducanumab (Aduhelm) had amyloid related imaging abnormalities (ARIA) which may be linked to brain bleeds/swelling.
- Labeling includes periodic brain magnetic resonance imaging (MRI) to monitor for ARIA.

References

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Revision History

Revision Date	Revision Summary
7/16/2021	New policy. Effective 8/15/2021

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Medication Policy Manual | **Policy No:** dru671

Topic: Nulibry, fosdenopterin | **Date of Origin:** August 15, 2021

Committee Approval Date: March 21, 2023 | **Next Review Date:** 2025

Effective Date: June 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Nulibry (fosdenopterin) is an intravenous medication used in the treatment of molybdenum cofactor deficiency type A.

Policy/Criteria

Most contracts require pre-authorization approval of Nulibry (fosdenopterin) prior to coverage.

I. Continuation of therapy (COT): Nulibry (fosdenopterin) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Nulibry (fosdenopterin) may be considered medically necessary when criteria A and B below are met.

A. A diagnosis of **molybdenum cofactor deficiency (MoCD) type A** that is confirmed by genetic testing, which shows a mutation in the MOCS1 gene.

AND

B. Attestation that the patient does not have advanced disease that is unlikely to respond to treatment, as evidenced by extensive cerebral necrosis on MRI or severe encephalopathy.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Nulibry (fosdenopterin) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Nulibry (fosdenopterin) will be authorized in quantities sufficient for up to a 30-day supply at a dose of up to 0.9 mg/kg once daily.

C. Authorization may be reviewed at least every 6 months. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, including disease stability or improvement.

IV. Nulibry (fosdenopterin) is considered investigational when used for all other conditions, including but not limited to:

A. Other types of MoCD (e.g., type B or C).

B. Sulfite oxidase deficiency.

Position Statement

Summary

- Molybdenum cofactor deficiency (MoCD) is an ultra-rare, autosomal recessive, inborn error of metabolism caused by disruption in molybdenum cofactor (MoCo) synthesis which is vital to prevent buildup of s-sulfocysteine, a neurotoxic metabolite of sulfite. Accumulation of this neurotoxin causes severe encephalopathy and intractable seizures with a high infant mortality rate.
- There are three types (A, B, and C) of MoCD, each caused by a different genetic mutation, but clinically indistinguishable.
- In patients with type A, a genetic mutation in the MOCS1 gene results in a deficiency in the production of cyclic pyranopterin monophosphate (cPMP), a necessary step in the biochemical pathway for MoCo production.
- Nulibry (fosdenopterin) is synthetic form of cPMP, allowing for MoCo synthesis to occur and prevent the buildup of the neurotoxic s-sulfocysteine.
- The intent of this policy is to cover Nulibry (fosdenopterin) for the indication and dose for which it has been shown to be safe and effective, for MoCD type A, as detailed in the coverage criteria.
- In the pooled analysis of three studies of patients with MoCD type A, Nulibry (fosdenopterin) improved survival compared with genotype matched controls.
- Patients with very advanced disease, including those with extensive cerebral necrosis, did not have a clinically relevant response to treatment.
- The diagnosis of MoCD type A may be challenging and requires genetic testing in combination with clinical features.

- Nulibry (fosdenopterin) may be covered in doses of up to 0.9 mg/kg/day, the highest dose studied in clinical trials. The safety and effectiveness of higher doses have not been established.
- The use of Nulibry (fosdenopterin) for any other indication, including other types of MoCD, is considered investigational.

Clinical Efficacy [1 2]

- Efficacy for Nulibry (fosdenopterin) was based on the pooled results of three low quality trials (MCD-201, MCD 202, and MCD 501); which enrolled a total of 13 patients with MoCD Type A. Survival results from the three studies were compared to untreated genotype-matched MoCD type A patients from a natural history study.
- The estimated survival probability was 84% in patients that received daily fosdenopterin, compared to 55% in the untreated genotype-matched cohort from a natural history trial, at year 3.
- In trial MCD-501, the only trial with published clinical results, efficacy was dependent on the severity of disease and extent of encephalopathy prior to initiation of the investigational version of fosdenopterin (recombinant cPMP).
    * Patients that were started on recombinant cPMP treatment prior to the onset of severe encephalopathy (n=3) were spared from significant disability. They acquired motor milestones and have "low normal" cognitive development, without sensory deficits or seizures. Speech delay and mild muscular hypotonia were noted in these patients.
    * Patients with advanced encephalopathy (n=3) had severe neurodevelopmental disability and there was no progress in motor skills.
    * Patients with extensive cerebral necrosis on MRI (n=3) received no benefit from the therapy, and it was discontinued, as their disease was deemed too severe to benefit from recombinant cPMP treatment.

Investigational Uses [2]

- The safety and effectiveness of Nulibry (fosdenopterin) in conditions other than MoCD type A have not been established.
- MoCD type B patients, enrolled in MCD-501, received no benefit from recombinant cPMP therapy. This is further validated by the mechanism of action of Nulibry (fosdenopterin), which would not be expected to provide benefit in MoCD type B or C.

Safety [3]

- During clinical trials the most frequent adverse events (>25% incidence) were catheter-related complications, pyrexia, viral infection, pneumonia, otitis media, vomiting, cough/sneezing, viral upper respiratory infection, gastroenteritis, bacteremia, and diarrhea.

Dosing [3]

- Nulibry (fosdenopterin) is administered intravenously once daily, in doses up to 0.9 mg/kg.
- Efficacy and dosing of Nulibry (fosdenopterin) in MoCD type A patients in doses higher than 0.9 mg/kg IV once daily has not been established.

References

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2. Schwahn BC, Van Spronsen FJ, Belaidi AA, et al. Efficacy and safety of cyclic pyranopterin monophosphate substitution in severe molybdenum cofactor deficiency type A: a prospective cohort study. *Lancet*. 2015;386(10007):1955-63. PMID: 26343839
3. Nulibry [Prescribing Information]. Boston, MA: Origin Biosciences; 2/2021

Revision History

Revision Date	Revision Summary
3/21/2024	No criteria changes with this annual review.
3/16/2023	No updates with this annual review.
3/18/2022	No updates with this annual review.
7/16/2021	New policy (effective 8/15/2021). Limits coverage to patients with genetically confirmed molybdenum cofactor deficiency (MoCD) type A without advanced disease, the setting in which clinical studies showed benefit.

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Medication Policy Manual

Policy No: dru672

Topic: Medications for Multiple Myeloma, other cancers, and other hematologic disorders

- Darzalex, daratumumab
- Darzalex Faspro, daratumumab and hyaluronidase-fihj
- Elrexfio (elranatamab-bcmm)
- Empliciti, elotuzumab
- Kyprolis, carfilzomib
- Ninlaro, ixazomib
- Pomalyst, pomalidomide
- Sarclisa, isatuximab-irfc
- Talvey (talquetamab-tgvs)
- Tecvayli, teclistamab-cqyv

Date of Origin: October 1, 2021

Committee Approval Date: September 19, 2024

Next Review Date: 2025

Effective Date: January 1, 2025

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Medications included in this policy are used primarily to treat multiple myeloma, but also include various other cancers, and other hematologic disorders.

Policy/Criteria

Most contracts require pre-authorization approval of Medications for Multiple Myeloma, other cancers, and other hematologic disorders ("Medications for MM") prior to coverage.

I. Continuation of therapy (COT): Medications for MM may be considered medically necessary for COT when criteria A and B below are met.

A. The patient is established on this therapy AND one of the following situations applies (criterion 1 or 2 below):

1. Prior to current health plan membership AND the medication was covered by another health plan.

PLEASE NOTE: *If the diagnosis is not listed in the coverage criteria below, written documentation of coverage must be provided, such as an approval letter or paid claim.*

OR

2. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

AND

B. If the diagnosis is listed in the 'Not Medically Necessary Uses' or 'Investigational Uses' coverage criteria below, documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria must be provided.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve) patients – Medically Necessary Uses:

Medications for multiple myeloma (MM) (as listed in Table 1) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that the applicable diagnosis-based criteria below are met.

Table 1.

Diagnosis	Coverable medication(s)	AND the following are met:
Kaposi sarcoma (KS)	- Pomalyst (pomalidomide)	**1.** If the KS is associated with acquired immune deficiency syndrome (AIDS-related), highly active antiretroviral therapy (HAART) was not effective.
Multiple myeloma (MM)	- Kyprolis (carfilzomib) - Darzalex (daratumumab) - Darzalex Faspro (daratumumab and hyaluronidase-fihj) - Elrexfio (elranatamab) - Empliciti (elotuzumab) - Ninlaro (ixazomib) - Pomalyst (pomalidomide) - Sarclisa (isatuximab-irfc) - Talvey (talquetamab) - Tecvayli (teclistamab-cqyv)	**1.** A diagnosis of MM. **AND** **2.** ***For Darzalex, Darzalex Faspro, Empliciti, Sarclisa only***: Will not be used in combination with another monoclonal antibody [such as listed in *Appendix 1*]. **AND** **3.** ***For Empliciti, Sarclisa, Ninlaro only:*** The MM is relapsed or refractory to at least one prior therapy. **AND** **4.** ***For Sarclisa only*:** The MM was not refractory to prior daratumumab *(refractory is defined as disease progression while on therapy, or within 60 days of the last dose).* **AND** **5.** ***For Tecvayli, Elrexfio, and Talvey only*:** Criteria a, b, and c below are met: **a.** There has been disease progression on or after at least four prior MM regimens including all of the following (i, ii, and iii): **i.** An anti-CD38 monoclonal antibody. **ii.** A proteosome inhibitor. **iii.** An immunomodulatory (IMID) agent. **b.** Tecvayli, Elrexfio, or Talvey will be used as monotherapy. **c.** For Tecvayli and Elrexfio only: No prior treatment with a therapy directed against B-cell maturation antigen (BCMA). (refer to *Appendix 1*)
Light chain amyloidosis (AL)	- Darzalex (daratumumab) - Darzalex Faspro (daratumumab and hyaluronidase-fihj)	**1.** A diagnosis of light chain amyloidosis (AL). **AND** **2.** The patient has had no prior therapy for AL (newly diagnosed). **AND** **3.** Daratumumab will be administered in combination with bortezomib, cyclophosphamide, and dexamethasone. **AND** **4.** No prior treatment with daratumumab.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers oral medications [including Ninlaro (ixazomib), Pomalyst (pomalidomide)] coverable only under the pharmacy benefit (as self-administered medications).

B. Regence Pharmacy Services considers injectable medications [including Kyprolis (carfilzomib), Darzalex (daratumumab), Darzalex Faspro (daratumumab and hyaluronidase-fihj), Empliciti (elotuzumab), Elrexfio (elranatamab-bcmm), Sarclisa (isatuximab-irfc), Talvey (talquetamab-tgvs) and Tecvayli (teclistamab-cqyv)] coverable only under the medical benefit (as provider-administered medications).

C. When pre-authorization is approved, each drug will be authorized as follows:

1. **Self-administered medications:** Up to the limits in Table 2 until disease progression.

2. **Provider-administered medications:** Up to FDA-recommended dose and frequency limits until disease progression.

Table 2. Self-Administered Medication Quantity Limits

Product	Quantity Limit
Ninlaro (ixazomib)	3 capsules per 28 days.
Pomalyst (pomalidomide)	- **MM:** Up to 21 capsules per 28 days. - **KS:** Up to 42 capsules per 28 days.

Key: KS=Kaposi sarcoma; MM=multiple myeloma

D. Authorization **may** be reviewed at least annually. For any ongoing authorization, clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

IV. Investigational Uses

A. Combination use of any medications in this policy, if specifically excluded in the coverage criteria above, including use of any two monoclonal antibodies for MM, including but not limited to Darzalex (daratumumab), Empliciti (elotuzumab), or Sarclisa (isatuximab-irfc) [see *Appendix 1*].

B. Unless otherwise specified in the coverage criteria above, medications included in this policy are considered investigational when used for all other conditions, due to lack of published data, lack of high-quality data, or lack of positive data.

Position Statement

Summary

- The intent of this policy is to cover medications for multiple myeloma, other cancers, and hematologic disorders ("medications for MM") in settings where they have been shown to be safe and effective, as detailed in the coverage criteria, with consideration for other available treatment options.
    * Where there is lack of proven additional benefit and/or lack of demonstrated health outcomes (such as overall survival or improved quality of life) relative to alternative therapies, use of medications for MM is not coverable ("not medically necessary" or "investigational").
    * It is important to note that the fact that a medication is FDA approved for a specific indication does not, in itself, make the treatment medically reasonable and necessary.
- Many of the clinical indications for medications for MM have been approved by the FDA and endorsed by clinical guidelines based on surrogate measures such as overall tumor response rate (ORR) and progression-free survival (PFS), measurements of tumor markers, which are not proven to accurately predict clinically important outcomes for MM, such as improved overall survival (OS), symptom control, or improved quality of life (QoL).
- Triplet MM regimens (drug regimens that combine medications from three different MM medication classes) have become the standard of care in treating MM. However, there are insufficient studies that compare regimens to clearly establish superiority of any one regimen or medication within a class (by mechanism of action).
- The safety and efficacy of monoclonal antibodies (mAbs) for MM in combination with other monoclonal antibodies for MM, or in conditions not included in coverage criteria (as listed above), have not been established. Currently, there are no published trials of the use of combination anti-MM monoclonal antibodies. Additional trials are ongoing.
- The National Comprehensive Cancer Network (NCCN) multiple myeloma guideline lists all drugs in this policy for use in MM in various settings, as well as other associated cancers and hematologic disorders. Choice of initial MM therapy is frequently based on transplant eligibility.
- Medications for MM are coverable for up to the dose and quantity as specified in the coverage criteria. For many medications for MM, they are given until disease progression, unacceptable toxicity, where others may be given for a specific duration (refer to coverage criteria). There is no conclusive additional benefit with higher doses or when given for longer durations except as specified in the coverage criteria.
- There are ongoing studies using medications for MM in a variety of other settings and other cancers. However, although initial evidence may be promising, the potential for clinical benefit in these conditions is still being investigated.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy

Multiple Myeloma (MM)

- Medications for multiple myeloma may be covered as detailed in the coverage criteria when there is documentation of a diagnosis of multiple myeloma.
- MM is a malignant neoplasm of plasma cells. The cells accumulate in bone marrow which leads to bone destruction and marrow failure. Skeletal destruction can lead to osteolytic lesions, osteopenia, and/or pathologic fractures. Bone pain is present at diagnosis in approximately 60% of patients. [1]
- MM is not curable using current approaches. Nearly all patients relapse on their initial treatment and require further therapy. The duration of response is generally shorter with each successive therapy. The five-year survival rate is approximately 52%. [2]
- Several subtypes of MM have been identified at the genetic and molecular level. Specific chromosomal translocations, deletions, and amplifications can be used to stratify disease risk (high, intermediate-, or standard-risk). [2]
- Choice of therapy may be based on several characteristics including whether the patient is a candidate for transplant, the disease risk category, genetic markers, and response to prior therapy. [2]
- Existing treatment approach usually involves use of multi-drug therapy regimens, referred to as doublet-, triplet-, or quad-therapy, with medications such as steroids, cytotoxic chemotherapy, immunomodulators (IMIDs), proteosome inhibitors (PIs), and monoclonal antibodies (mAbs). However, there is insufficient evidence to establish the safety or efficacy of the use of combination of monoclonal antibodies for MM.

- The evidence for some medications for MM is limited to the relapsed/refractory (r/r) setting, such as with the proteosome inhibitor, Ninlaro (ixazomib), as detailed in the coverage criteria. Similarly, Tecvayli (teclistamab-cqyv) is only coverable as a monotherapy for MM refractory to multiple other therapies.
- There is insufficient evidence that any one medication for MM (by mechanism of action/class) is superior to another. There is limited comparative efficacy for MM.

Pomalyst (pomalidomide) for MM

- Approval of pomalidomide was based on a single, open-label trial in 221 patients with r/r MM, comparing pomalidomide alone vs. pomalidomide plus low-dose dexamethasone. [3, 4]
    * Patients enrolled in the trial had a minimum of two prior MM therapies. Prior therapies must have included lenalidomide, and bortezomib.
    * ORRs were 7.4% and 29.2% with pomalidomide and pomalidomide plus dexamethasone, respectively.
- A second open-label trial compared pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone in 455 refractory MM patients. Subjects in the pomalidomide group had a longer median overall survival at 15.4 months of follow-up (13.1 vs. 8.1 months, HR 0.75, p = 0.009). Confidence in this result is reduced by high attrition rate during the trial, the lack of blinding, and crossover between treatment groups. [5]

Kyprolis (carfilzomib) for MM

- Initial approval of carfilzomib was based on one single-arm trial in 266 subjects that evaluated ORR in patients with relapsed MM. [6]
    * Patients enrolled in the trial had received at least two prior therapies (including bortezomib and an immunomodulator [IMID], lenalidomide or thalidomide).
    * The median number of prior therapies was five and 95% were refractory to their last line of therapy.
    * The study reported an ORR of 23.7% (17.7% partial responses, 4.9% very good partial response, and 0.4% complete response).
    * There is low confidence in the evidence from the study because a cause effect relationship cannot be established due to the lack of comparator.
- A single large, randomized, open-label trial evaluated the combination of carfilzomib plus lenalidomide/dexamethasone vs. lenalidomide/dexamethasone (control group) in relapsed MM. Subjects enrolled in the trial had between one and three prior therapies. [7]
    * The median PFS was 26.3 months and 17.6 months in the carfilzomib and control arm, respectively. Corresponding ORRs were 87.1 and 66.7%.
    * Although a lower HR for death was observed in the treatment group (HR 0.79, p = 0.04), survival data is not mature; the durability and clinical meaningfulness of this difference is not fully elucidated.
    * There is low confidence in these data due to high attrition (~30%) and lack of blinding.
- Carfilzomib/dexamethasone was shown to improve median OS relative to bortezomib/dexamethasone as a subsequent therapy for r/r MM. The clinical relevance of this finding is uncertain as the majority of patients had relapsed after prior bortezomib,

which likely disadvantages the bortezomib treatment arm. However, it is supportive of the efficacy of carfilzomib as a subsequent proteosome inhibitor therapy for MM. [8]

Ninlaro (ixazomib) for MM

- The evidence for efficacy for ixazomib comes from a single randomized, controlled trial that demonstrated improvements in PFS, a surrogate endpoint, in patients who had r/r MM who had received at least one prior line of therapy. [9, 10]
    - All patients had at least one prior therapy for MM. A majority had prior bortezomib or melphalan. Patients refractory to lenalidomide or proteosome inhibitors were excluded.
    - Ixazomib improved PFS vs. lenalidomide/dexamethasone alone (20.6 vs 14.7 months).
    - A more recent RCT evaluated ixazomib as a maintenance therapy after hematopoietic stem cell transplant (HSCT). [11] An interim analysis reported a PFS advantage relative to placebo; however, OS data are not mature. The trial remains blinded and is ongoing. Ixazomib is not currently approved for use in this treatment setting.

Farydak (panobinostat) for MM

- Farydak (panobinostat) was a histone deacetylase inhibitor that received accelerated approval for relapsed or refractory MM. It was withdrawn from the US commercial market in early 2022. [12, 13, 14]
- The manufacturer is making Farydak (panobinostat) available to certain MM patients in the US who are currently receiving it. Refer to www.farydak.com/notice/ for more information.

Darzalex (daratumumab) for MM

- Darzalex (daratumumab) and Darzalex Faspro (daratumumab and hyaluronidase-fihj) are CD38-directed monoclonal antibody products for the treatment of MM. Darzalex is given intravenously (IV), while Darzalex Faspro is given subcutaneously (SC). [15, 16]
- Darzalex (daratumumab) demonstrated improved overall survival (OS) when added to a backbone regimen of either Revlimid (lenalidomide) plus dexamethasone (Rd) or Velcade (bortezomib) plus dexamethasone (Vd) in patients with relapsed or refractory MM relative to either Rd or Vd alone.
- Although there may be differences in FDA-approved indications between products, the guidelines support interchangeability. There are ongoing studies evaluating Darzalex Faspro (daratumumab and hyaluronidase-fihj) in combination with other MM medications (other than those regimens that have already been approved as safe and effective). The NCCN MM guideline footnotes Darzalex Faspro (daratumumab and hyaluronidase-fihj) as being alternative to Darzalex (daratumumab) across all of the settings for which Darzalex (daratumumab) is recommended. [2]
- Darzalex (daratumumab) is given in a dose of 16 mg/kg IV, whereas Darzalex Faspro (daratumumab and hyaluronidase-fihj) is given in a dose of 1,800 mg – 30,000 units SC. [15, 16]

Darzalex (daratumumab) intravenous (IV) formulation:

As monotherapy for relapsed and/or refractory MM:

- The efficacy of Darzalex (daratumumab) IV is based on two single-arm, unblinded clinical studies in patients with r/r MM. Patients had received a median of 4-5 prior lines of therapy. [17, 18]
    - Common prior therapies included Velcade (bortezomib), Revlimid (lenalidomide), and Pomalyst (pomalidomide).
    - A majority of patients were refractory to both a proteosome inhibitor (PI) [such as Velcade (bortezomib)] and an immunomodulatory agent (iMiD) [e.g., Revlimid (lenalidomide)].
    - Efficacy was evaluated based on ORR. The ORR in one study was 29.2% and 36% in the second study.

As an add-on to standard therapy for relapsed and/or refractory MM:

- Two RCTs evaluated Darzalex (daratumumab) IV as an add-on to backbone therapy with either Revlimid (lenalidomide) plus dexamethasone (Rd), or Velcade (bortezomib) plus dexamethasone (Vd) in patients with r/r MM who had at least one prior therapy. [20, 21]
    - In a final analysis of these two trials a significant improvement in OS was reported with add-on Darzalex (daratumumab) relative to Rd or Vd alone. [50, 51]
    - The following flaws may lower confidence in the reported results: Neither study was blinded, and performance bias due to high attrition cannot be ruled out.
- An uncontrolled (single-arm), open-label trial evaluated Darzalex (daratumumab) IV as an add-on to backbone therapy with dexamethasone plus Pomalyst (pomalidomide). Patients enrolled in the study had a median of four prior MM therapies. [22]
    - The ORR was 59.2%, with 5.8% complete responses. Although results may appear impressive relative to historical controls, it cannot be concluded that add-on Darzalex (daratumumab) IV improves any clinical outcome relative to dexamethasone and Pomalyst (pomalidomide) alone.
    - Evidence from this trial is of very low quality due to the lack of comparator and use of an unvalidated surrogate endpoint.

As a primary MM therapy when autologous stem cell transplant is not an option:

- A randomized, open-label trial showed improved PFS at 18 months with Velcade (bortezomib)/melphalan/prednisone (BMP) plus Darzalex (daratumumab) IV vs. BMP alone, in newly diagnosed MM not eligible for an autologous stem cell transplant (ASCT). [23]
    - Patients enrolled in the trial either had coexisting conditions which precluded them from receiving high-dose chemotherapy with ASCT, or were 65 years of age or older (92% of the population).
    - The 18-month PFS was 71.6% [95% CI, 65.5, 76.8] and 50.2% [43.2, 56.7%] in the daratumumab and control groups, respectively. Median follow up at the time of the interim analysis was 16.5 months.

Darzalex Faspro (daratumumab and hyaluronidase-fihj) subcutaneous (SC) formulation: [16]

- The safety and efficacy of Darzalex Faspro (daratumumab and hyaluronidase-fihj) SC is based on previous Darzalex (daratumumab) IV studies. Pharmacokinetic studies and small, single-arm, observational trials evaluating PFS in the following settings were used as confirmatory evidence for Darzalex Faspro (daratumumab and hyaluronidase-fihj):
    * Newly diagnosed MM in combination with Velcade (bortezomib), melphalan, and prednisone.
    * r/r MM in combination with Revlimid (lenalidomide) and dexamethasone.
    * r/r MM as a monotherapy after disease progression on at least three prior therapies (including a proteosome inhibitor and immunomodulator), or progression after at least two prior PI and iMiD combination regimens.

Sarclisa (isatuximab-irfc) for MM

- Sarclisa (isatuximab-irfc) is an intravenously administered CD38-directed monoclonal antibody. Its mechanism of action is similar to that of Darzalex (daratumumab) IV.
- The initial FDA approval was based on low-quality data from a single, open-label (non-blinded), randomized, controlled trial in r/r MM. The trial compared Sarclisa (isatuximab-irfc), Pomalyst (pomalidomide) and dexamethasone (IPD) with PD alone. The overall confidence in the study results is limited due to several concerns (lack of blinding, potential imbalance in populations, and high rate of differential attrition). [24, 25]
    * Patients had been treated with a minimum of two prior MM therapies.
    * All patients had no response to prior Revlimid (lenalidomide) and proteosome inhibitors (used either separately or in combination). Non-response was defined as disease progression on or within 60 days, intolerance to Revlimid (lenalidomide) or the proteosome inhibitor, or disease progression within 6 months after achieving at least a partial response.
    * Patients with prior use of Pomalyst (pomalidomide) were not allowed in the study, nor were those with disease refractory to prior therapy with daratumumab, another CD-38 monoclonal antibody. *Refractory was defined as having achieved an initial response with subsequent disease progression while on therapy, or progression within 60 days of the last dose.*
    * The trial reported a PFS benefit with the addition of Sarclisa (isatuximab-irfc) to PD, a surrogate endpoint. OS will be analyzed as a secondary endpoint; however, no significant difference in survival between the study arms has been noted to date.

Empliciti (elotuzumab) for MM

- Empliciti (elotuzumab) is an intravenously administered SLAMF7-directed immunostimulatory monoclonal antibody for the treatment of r/r MM.
- The initial evidence for efficacy of Empliciti (elotuzumab) was based on a single, phase 3, randomized, open-label trial in patients who had received one to three prior therapies for MM [ELOQUENT-2 (NCT01239797)]. [26] The median number of prior treatments was two. Velcade (bortezomib) was the most common prior therapy (70%), followed by melphalan (65%), Thalomid (thalidomide) (48%), and Revlimid (lenalidomide) (6%).

Empliciti (elotuzumab) improved PFS, a surrogate endpoint. However, the effect of Empliciti (elotuzumab) on clinically relevant outcomes such as overall survival or quality of life is not known.

  * Empliciti (elotuzumab) plus Revlimid (lenalidomide)/dexamethasone was compared to Revlimid (lenalidomide)/dexamethasone alone.
  * Elotuzumab resulted in a 4.5-month PFS advantage compared to Revlimid (lenalidomide) and dexamethasone alone (19.4 months vs 14.9 months, respectively).

- Subsequently, Empliciti (elotuzumab) was studied in combination with Pomalyst (pomalidomide)/dexamethasone vs. Pomalyst (pomalidomide)/dexamethasone in a single, phase 3, randomized, open-label trial (n=117) in patients with r/r MM [ELOQUENT-3]. [27] Empliciti (elotuzumab) improved ORR, as well as PFS, surrogate endpoints. However, the effect of Empliciti (elotuzumab) on clinically relevant outcomes such as overall survival or quality of life is not known.
  * The median number of prior treatments was three. Prior therapies included stem cell transplant (55%), Velcade (bortezomib) (100%), Revlimid (lenalidomide) (99%), cyclophosphamide (66%), melphalan (63%), Kyprolis (carfilzomib) (21%), and Darzalex (daratumumab) IV (3%).
  * The patient population was highly-refractory to prior therapies: Revlimid (lenalidomide)-refractory (87%); proteosome inhibitor-refractory (80%); Revlimid (lenalidomide)- and proteosome inhibitor-refractory (70%).
  * Empliciti (elotuzumab) improved PFS by 5.58-months vs. Pomalyst (pomalidomide)/dexamethasone alone (10.25 months vs 4.67 months, respectively).
- A smaller, preliminary (phase 2) trial evaluated elotuzumab as an add-on to Velcade (bortezomib) plus dexamethasone. [28, 29] A 2.8-month PFS advantage was reported.

Blenrep (belantamab mafodotin-blmf) for MM [30, 38]

- Blenrep (belantamab mafodotin-blmf) was recently withdrawn from the market and is no longer available. The reason for withdrawal is failure to show a clinical benefit over standard therapy in the trial intended to confirm efficacy for regular FDA approval.
- Patients who are already enrolled in the Blenrep REMS program will have the option to enroll in a Compassionate use program through the manufacturer. (www.blenrep.com)

Pepaxto (melphalan flufenamide) for MM

- Pepaxto (melphalan flufenamide) has been withdrawn from the market because harms were found to exceed any potential for benefit in MM.

Tecvayli (teclistamab-cqyv) and Elrexfio (elranatamab-bcmm) for MM [47-49, 54, 55]

- Tecvayli (teclistamab-cqyv) and Elrexfio (elranatamab-bcmm) are intravenously administered bispecific B-cell maturation antigen (BCMA)-directed T-cell engagers for the treatment of multi-refractory MM.
- Tecvayli (teclistamab-cqyv) and Elrexfio (elranatamab-bcmm) each received FDA accelerated approval based on small, single-arm observational studies that evaluated objective response rate (ORR) in patients with triple class exposed (immunomodulator,

proteosome inhibitor, CD38-directed monoclonal antibody) patients with relapsed or refractory MM.

  * Patients in each of the studies had a median of five prior therapies.
  * The studies evaluated tumor response as the primary surrogate endpoint:
    - *Tecvayli (teclistamab-cqyv):* The ORR was 62%, with 28% of subjects having a complete response or better.
    - Elrexfio (elranatamab-bcmm): The ORR was 58%, with 26% of subjects having a complete response or better.

- It has not been determined whether Tecvayli (teclistamab-cqyv) or Elrexfio (elranatamab-bcmm) improve any clinically important outcomes (e.g., overall survival), or whether the potential for benefit is greater than the risks of therapy.
- Access to both Tecvayli (teclistamab-cqyv) and Elrexfio (elranatamab-bcmm) is restricted via Risk Evaluation and Mitigation Strategies (REMS).

Talvey (talquetamab-tgvs) for MM [52, 53]

- Talvey (talquetamab-tgvs) is an intravenously administered bispecific GPRC5D-directed T-cell engager for the treatment of MM.
- Talvey (talquetamab-tgvs) received FDA accelerated approval based on a small, single-arm observational study that evaluated objective response rate (ORR) in patients with triple class exposed (immunomodulator, proteosome inhibitor, CD38-directed monoclonal antibody) patients with relapsed or refractory MM.
  * Patients enrolled in the study had a median of five prior MM therapies.
  * The ORR was 73%, with 35% of subjects having a complete response or better.
- It has not been determined whether Talvey (talquetamab-tgvs) improves any clinically important outcome (e.g., overall survival) or whether the potential for benefit is greater than the risks of therapy.
- Access to Talvey (talquetamab-tgvs) is restricted via the Talvey Risk Evaluation and Mitigation Strategy (REMS).

Kaposi Sarcoma (KS)

- The approval of Pomalyst (pomalidomide) in KS is based on an observational trial that followed 18 patients who were HIV-positive, and 10 patients who were HIV-negative. The trial evaluated tumor response as the endpoint. [35]
- The trial excluded patients with symptomatic pulmonary or visceral KS.
- The majority (75%) of subjects in the trial had received prior chemotherapy for their KS. Patients who were HIV-positive also had to have been receiving highly active anti-retroviral therapy (HAART) for a minimum of two to three months without regression of their KS prior to being treated with pomalidomide. [35]
- The NCCN AIDS-related KS guideline recommends liposomal doxorubicin as the preferred front-line therapy for KS. Treatment in HIV-negative patients parallels treatment in the HIV-positive population. Pomalidomide is a preferred regimen after failure of front-line chemotherapy. [36]

Light chain amyloidosis (AL)

- The approval (FDA Accelerated approval) of Darzalex Faspro (daratumumab and hyaluronidase-fihj) SC in light chain amyloidosis (AL) is based on an open-label RCT [ANDROMEDA] that evaluated an unvalidated surrogate as the primary endpoint. As per FDA Accelerated approval regulations, additional evidence is needed to confirm there is a clinical benefit for continued approval. [16]
    * The trial compared the addition of Darzalex Faspro to Velcade (bortezomib)/ cyclophosphamide/dexamethasone (D-VCd) with VCd alone.
    * Patients enrolled in the study had newly diagnosed, measurable (hematologic) disease that affected at least one organ (e.g., heart, liver, kidney).
    * Patients with certain cardiac disease (e.g., NYHA Class IIIB and IV) where not allowed to enroll in the trial.
    * Per protocol, therapy was administered for a maximum of two years, or until there was disease progression.
    * Complete hematologic response HemCR, the primary endpoint, was achieved in 42% and 13% of the D-VCd and VCd treatment groups, respectively.
    * HemCR has not been shown to accurately predict any clinically important outcome (e.g., improved survival or quality of life).
- The NCCN Systemic Light Chain Amyloidosis guideline lists D-VCd among the preferred treatment options for front-line use in AL. [44]

Safety [37]

- Overall, medications for MM, by class/mechanism of action, appear to have similar safety profiles (based on indirect comparisons). There is no reliable evidence to allow conclusion that any one medication for MM (by class) is safer or more tolerable that another, given lack of comparative safety data. Common adverse events include:
    * IMIDs: Neutropenia, fatigue, anemia, constipation, nausea, diarrhea, dyspnea, upper respiratory tract infections, back pain, and pyrexia. Boxed warnings for embryo-fetal toxicity, venous thromboembolism, and hematologic toxicity. A restricted distribution program (Risk Evaluation and Management Strategy, "REMS") is in place to prevent accidental fetal exposure. Doses may be modified for hematologic toxicity.
    * Proteosome inhibitors: gastrointestinal toxicity, thrombocytopenia, and peripheral neuropathy; severe: cardiac toxicity.
    * Monoclonal antibodies: infusion-related reactions, neutropenia, upper respiratory tract infections, and diarrhea. Premedication with antihistamines, antipyretics, and corticosteroids is recommended. Of note: The safety of Darzalex Faspro (daratumumab and hyaluronidase-fihj) parallels that of the intravenous product.
    * Alkylating Agents: bone marrow suppression (including anemia, leukopenia, lymphocytopenia, neutropenia, and thrombocytopenia), gastrointestinal toxicity (including nausea and vomiting), renal toxicity, fatigue. Boxed warnings for severe marrow suppression leading to infection or bleeding, hypersensitivity reactions (including anaphylaxis), and potential secondary malignancy.

- Overall tolerability of some medications for MM may limit utility:
    * HDAC inhibitor Farydak (panobinostat): labeling contains a boxed warning for severe diarrhea (25% severe), and cardiac toxicity, including severe and fatal cardiac ischemic events, as well as severe arrhythmias. Therapy should be interrupted at the onset of moderate diarrhea (4 to 6 stools per day). Other serious toxicities include hemorrhage, hepatotoxicity, and embryo-fetal toxicity. Electrolyte abnormalities are also common. [13]
    * Tecvayli (teclistamab-cqyv): labeling contains a boxed warning for cytokine release syndrome (CRS) and neurological toxicity, including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS). Use is restricted through the Tecvayli Risk Evaluation and Mitigation Strategy (REMS). [47-49]
    * Xpovio (selinexor): is associated with significant toxicity, need for dose modifications, and treatment-related deaths (see Xpovio policy for details). [39-42]

Appendix 1: Classification of Medications used for Multiple Myeloma		
Chemotherapy	**Immunomodulators (IMIDs)**	**Proteosome Inhibitors (PIs)**
- cyclophosphamide - doxorubicin - Doxil (liposomal doxorubicin) - melphalan HCl (generic, Evomela) - vincristine	- Revlimid (lenalidomide) - Pomalyst (pomalidomide) - Thalomid (thalidomide)	- bortezomib (generic Velcade) - Kyprolis (carfilzomib) - Ninlaro (ixazomib)
Exportin 1 inhibitor	**Anti-BCMA therapy**	**Monoclonal Antibodies (mAbs)**
- Xpovio (selinexor)	- Abecma (idecabtagene vicleucel) - Carvykti (ciltacabtagene autoleucel) - Elrexfio (elranatamab-bcmm) - Tecvayli (teclistamab-cqyv)	- Anti-CD38 - Darzalex (daratumumab) - Sarclisa (isatuximab-irfc) - Anti-SLAMF7 - Empliciti (elotuzumab)
GPRC5D-Directed therapy		
- Talvey (talquetamab-tgvs)	-	-

Table 3. Investigational Uses	
There is insufficient evidence to establish the safety or efficacy of the medications for MM (as listed below) for the treatment of the listed conditions. Additional studies are ongoing for many of these conditions. [43]	
Front-line treatment of MM	Empliciti (elotuzumab), Ninlaro (ixazomib), and Sarclisa (isatuximab-irfc) are being studied in the front-line multiple myeloma setting. However, the evidence is considered preliminary.
Sequential use of BCMA-directed agents	There is unpublished, low-quality evidence suggesting Elrexfio (elranatamab) may have some activity in patients who had prior exposure to BCMA-directed therapy; however, data is limited to tumor responses in small numbers of patients. Additional information is needed to establish efficacy in these patients. Sequential use of BCMA-directed therapies remains investigational.
Myelofibrosis	There are several small, published studies that evaluate the use of Pomalyst (pomalidomide) in patients with myelofibrosis. Several other medications for MM are also being studied. The evidence is considered insufficient at this time.
Smoldering multiple myeloma	There are several ongoing studies to evaluate various MM therapies [Kyprolis (carfilzomib), Darzalex (daratumumab), Darzalex Faspro (daratumumab and hyaluronidase-fihj), Empliciti (elotuzumab), Ninlaro (ixazomib), and Sarclisa (isatuximab-irfc)] in smoldering plasma cell myeloma. The evidence is considered insufficient at this time.
Systemic light chain amyloidosis (AL), in the absence of multiple myeloma	- Pomalyst (pomalidomide) in combination with dexamethasone is one of many potential treatment regimens listed in the NCCN Systemic Light Chain Amyloidosis guidelines; however, the guidelines state that optimal therapy for systemic light chain amyloidosis remains unknown and treatment in the context of a clinical trial is strongly encouraged when possible. Other listed treatment options include, but are not limited to, cyclophosphamide/thalidomide/dexamethasone, dexamethasone/alpha-interferon, oral melphalan/dexamethasone, and thalidomide/dexamethasone. [44] - There are several ongoing studies listed in clinicaltrials.gov that are designed to evaluate Sarclisa (isatuximab-irfc) in other disease settings including amyloidosis. There are no results posted to date.
Waldenström's macroglobulinemia	- There are ongoing trials that are studying Pomalyst (pomalidomide) and Kyprolis (carfilzomib) in Waldenström's macroglobulinemia. There is no published data supporting the safety and efficacy of Pomalyst (pomalidomide) in these populations. - There is currently insufficient evidence to support the use of Kyprolis (carfilzomib) in combination with rituximab and dexamethasone for the treatment of Waldenström's macroglobulinemia. Although Kyprolis (carfilzomib)/rituximab/dexamethasone is listed in NCCN guidelines as a category 2A recommendation, the only information to date consists of a single-center, uncontrolled phase 2 study in 31 patients. [45] Well-designed studies are necessary to establish efficacy and benefit in these populations.
Solid tumors	There are also several ongoing trials that are studying Pomalyst (pomalidomide) in soft tissue sarcoma. There is no published data supporting the safety and efficacy of Pomalyst (pomalidomide) in these populations.

Cross References
Products with Therapeutically Equivalent Biosimilars/Reference Products, Medication Policy Manual, Policy No. dru620
Chimeric Antigen Receptor (CAR) T-cell Therapies, Medication Policy Manual, Policy No. dru523
Xpovio, selinexor, Medication Policy Manual, Policy No. dru607

Codes	Number	Description
HCPCS	J9145	Injection, daratumumab (Darzalex), 10 mg
HCPCS	J9144	Injection, daratumumab and hyaluronidase-fihj (Darzalex Faspro), 10 mg
HCPCS	J9176	Injection, elotuzumab (Empliciti), 1 mg
HCPCS	J1323	Injection, elranatamab-bcmm (Elrexfio), 1 mg
HCPCS	J9047	Injection, carfilzomib (Kyprolis), 1 mg
HCPCS	J9227	Injection, isatuximab-irfc (Sarclisa), 10 mg
HCPCS	J9380	Injection, teclistamab-cqyv (Tecvayli), 0.5 mg
HCPCS	J3055	Injection, talquetamab-tgvs (Talvey), 0.25 mg

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Revision History

Revision Date	Revision Summary
09/19/2024	Removed prior chemotherapy step for treatment of Kaposi sarcoma with pomalidomide (Pomalyst) based on practical considerations and improved member access.
6/20/2024	No criteria changes with this annual review.
3/21/2024	No criteria changes with this annual review.
12/7/2023	Coverage for Elrexfio (elranatamab-bcmm) was added to the policy when used as a monotherapy for patients with MM who have had at least four prior MM regimens which must have included an anti-CD38 mAb, a proteosome inhibitor, and an immunomodulatory agent when there has been no prior therapy with therapy directed against BCMA. Coverage for Talvey (talquetamab-tgvs) was added to the policy when used as a monotherapy for patients with MM who have had at least four prior MM regimens which must have included an anti-CD38 mAb, a proteosome inhibitor, and an immunomodulatory agent.
6/15/2023	No changes to policy criteria with this annual update.
3/16/2023	• Blenrep (belantamab mafodotin) was removed from the policy because the manufacturer has ceased marketing of this product in the U.S. • Coverage for Tecvayli (teclistamab-cqyv) was added to the policy when used as a monotherapy for patients with MM who have had at least four prior MM regimens which must have included an anti-CD38 mAb, a proteosome inhibitor, and an immunomodulatory agent when there has been no prior therapy with therapy directed against BCMA.
6/17/2022	Effective 9/1/2022: • Farydak (panobinostat) was removed from this policy because the manufacturer has ceased marketing of this product in the US. • Pepaxto (melphalan flufenamide) removed from policy due to withdrawal from the market. *Note: Revisions were made to update to current standard policy language; however, there was no change to the intent of this policy.*
10/15/2021	Pepaxto (melphalan flufenamide) changed to investigational for all indications due to a safety signal that indicates numerically higher incidence of death with melphalan flufenamide versus standard of care.
7/16/2021	New combination policy (effective 10/1/2021): • The individual Multiple Myeloma policies were combined, with the exception of selinexor (Xpovio, dru607) and idecabtagene vicleucel (Abecma; a newer CAR-T therapy, dru523). • Revlimid will no longer require pre-authorization. • The newly FDA approved Pepaxto (melphalan flufenamide) added to policy. The use of Pepaxto for multiple myeloma will be considered not medically necessary and therefore not covered due to lack of proven additional benefit versus lower-cost intravenous melphalan HCl.

Revision Date	Revision Summary
	• Added coverage criteria for Darzalex (daratumumab), Darzalex Faspro (daratumumab and hyaluronidase-fihj) in systemic light chain amyloidosis, a newly FDA approved indication. • Coverage criteria now explicitly list that combination of any two monoclonal antibodies (Darzalex, Empliciti, Sarclisa; per Appendix 1) is not coverable. No change to intent. • Investigational Uses were simplified (any use without coverage criteria is "Investigational"). • Clarification of quantity limits, for operational consistency. • Removed metastatic castration-resistant prostate cancer (for lenalidomide) from the list of 'Not Medically Necessary' uses (this indication was also listed under 'Investigational Uses').

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Medication Policy Manual | **Policy No:** dru673

Topic: Jemperli, dostarlimab | **Date of Origin:** November 15, 2021

Committee Approval Date: September 19, 2024 | **Next Review Date:** 2025

Effective Date: January 1, 2025

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Jemperli (dostarlimab) is an intravenously infused immunotherapy that is used in the treatment of advanced endometrial cancer.

Policy/Criteria

Most contracts require pre-authorization approval of Jemperli (dostarlimab) prior to coverage.

I. Continuation of therapy (COT): Jemperli (dostarlimab) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Jemperli (dostarlimab) may be considered medically necessary when criteria A through C below are met:

A. A confirmed diagnosis of **endometrial carcinoma**, advanced (not curable with resection).

AND

B. No prior programmed death receptor-1 (PD-1) blocking antibody (PD-1 inhibitor) or programmed death-ligand 1 (PD-L1) blocking antibody therapy (*see Appendix 1*).

AND

C. Jemperli (dostarlimab) will be used in one of the following two settings (1 or 2):

1. **Front line:** As part of a front-line regimen, when both criteria below are met (a and b):

a. No prior systemic therapy for endometrial carcinoma in the advanced treatment setting.

AND

b. Jemperli (dostarlimab) will be initiated in combination with carboplatin and paclitaxel.

OR

2. **Subsequent therapy**, when all criteria below are met (a to c):

a. Disease progression on or following prior treatment with a platinum-based chemotherapy regimen.

AND

b. The tumor is mismatch repair deficient (dMMR) by immunohistochemistry (IHC) or polymerase chain reaction (PCR) testing.

AND

c. Jemperli (dostarlimab) will be used as monotherapy.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Jemperli (dostarlimab) coverable only under the medical benefit (as a provider- administered medication).

B. When pre-authorization is approved, Jemperli (dostarlimab) may be approved in the quantities below:

Setting	Quantity Limit	Duration
Endometrial cancer, front-line setting initiated with chemotherapy	Initial: 500 mg IV every three weeks for six doses, followed by 1,000 mg IV every six weeks Continued: 1,000 mg IV every six weeks	Initial / Continued: 24 weeks, until disease progression
Endometrial cancer, subsequent-line setting as monotherapy	Initial: 500 mg IV every three weeks for four doses, followed by 1,000 mg IV every six weeks Continued: 1,000 mg IV every six weeks	Initial / Continued: 24 weeks, until disease progression

C. Reauthorization: Authorization **shall** be reviewed at least every 24 weeks for documented benefit. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met. Specifically, documentation that the medication is providing clinical benefit, including disease stability or improvement, and lack of disease progression, based on an assessment of change in tumor burden. If there is documentation of potential disease progression, a shortened authorization (up to three months)

may be approved to allow time for clarification of response to Jemperli (dostarlimab), including clinical re-evaluation of the patient and reimaging.

PLEASE NOTE: Additional doses of Jemperli (dostarlimab) will not be authorized without a documented recent assessment by the treating provider (such as oncologist) with objective evidence of response to therapy, such as by re-imaging and use of iRECIST criteria.

IV. Jemperli (dostarlimab) is considered investigational when used for all other conditions, including but not limited to:

A. Microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) tumors [unless specified in the sections above].

Position Statement

Summary

- Jemperli (dostarlimab) is a human programmed death receptor-1 (PD-1) blocking monoclonal antibody (immunotherapy) used in the treatment of specific types of cancers.
- The intent of this policy is to cover Jemperli (dostarlimab) in settings where it has been shown to be safe and effective, as detailed in the coverage criteria, with consideration for other available treatment options.
  * Where there is lack of proven additional benefit and/or lack of demonstrated health outcome (such as overall survival or improved quality of life) relative to alternative therapies, use of dostarlimab (Jemperli) alone or in combination with other therapies is not coverable ("not medically necessary" or "investigational").
  * It is important to note that the fact that a medication is FDA approved for a specific indication does not, in itself, make the treatment medically reasonable and necessary.
- Jemperli (dostarlimab) is FDA approved for use in the following conditions; however, the health plan considers these uses to be "investigational" (not covered) as Jemperli (dostarlimab) has not demonstrated any health benefit, based on the currently available evidence:
  * MSI-H tumors, other than endometrial carcinoma *(as described in the Clinical Efficacy section below).*
- Many of the clinical indications for immunotherapies (PD-1, PD-L1, and others) have been approved by the FDA and endorsed by clinical guidelines based on surrogate measures such as overall tumor response rate (ORR) and progression-free survival (PFS), which are not proven to accurately predict clinically important outcomes such as improved overall survival or improved quality of life.
- National Comprehensive Cancer Network (NCCN) guidelines recommend Jemperli (dostarlimab) as a potential option in each of the treatment settings listed in the coverage criteria. In general, NCCN recommendations parallel the FDA approved indications.

- The PD-1 and PD-L1 inhibitors have the potential to cause immune-mediated adverse reactions that can result in pneumonitis, colitis, hepatitis, endocrinopathies, and nephritis.
- Jemperli (dostarlimab) is coverable up to the dose and quantity that is specified in the coverage criteria. It is administered until disease progression or unacceptable toxicity.
- Optimal sequencing of chemotherapy and immunotherapy in many cancers is unknown or the data is evolving. At this time, sequential use of immunotherapies is not supported by current evidence. Specifically, there is no evidence to support the sequential use of different PD-1 or PD-L1 inhibitors once there is disease progression on prior PD-1 or PD-L1 inhibitor therapy, as well as use of adjuvant PD-1/PD-L1 inhibitor after neoadjuvant PD-1/PD-L1 inhibitor therapy (unless explicitly listed in the coverage criteria). Therefore, the use of sequential courses of PD-1/PD-L1 immunotherapy is not coverable.
- There are ongoing studies using Jemperli (dostarlimab) in a variety of other cancers. However, although initial evidence may be promising, the potential for clinical benefit in these conditions is still being investigated.
- *Reauthorization Criteria*: When coverage criteria are met, Jemperli (dostarlimab) is authorized for six months (24 weeks) of therapy, after which time documentation must be provided to establish that the medication is effective. Specifically, there must be documentation of clinical benefit, including disease stability or improvement and there is a lack of disease progression, based on an assessment of change in tumor burden. Documentation of benefit must include an assessment of the most recent imaging ("restaging scans") and/or re-biopsy by the treating oncologist.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy

ENDOMETRIAL CANCER (EC)

- *Disease Background [1]*
  - Endometrial cancer (EC) is the most commonly occurring gynecologic cancer in the U.S. Most cases (75%) are diagnosed at an early stage and can be cured with surgery. However, approximately 25% are diagnosed in advanced stages.
  - For advanced disease, first-line therapy with surgery and platinum-containing chemotherapy (standard of care) results in overall survival ranging between 13 and 29 months with tumor response rates of 40 to 62%.
  - Upon disease progression in the advanced disease setting, tumor response rates are generally in the 7 to 14% range with single-agent chemotherapy.
  - It is estimated that approximately 25% to 30% of endometrial tumors may have a high frequency of somatic mutations which are attributable to deficiencies in DNA mismatch repair (dMMR) making these tumors a possible target of immunotherapies such as programmed death receptor-1 inhibitors.
- The efficacy of Jemperli (dostarlimab) was evaluated in a small, non-comparative, non-blinded study (GARNET) that evaluated tumor response in patients with advanced EC. *[2 3]* The quality of this data is poor due to the lack of randomization, blinding, and comparator. Furthermore, tumor response is not predictive of improvement in any clinically relevant outcome.
  - The population evaluated for the EC indication was a specific cohort from a larger study that included patients with many different types of solid tumors. All patients in the EC cohort had mismatch repair deficient (dMMR) EC that could not be cured with surgery (advanced or metastatic disease) and had progressed on or after platinum doublet therapy.
  - Tumor response (objective response rate) was 42% with 12.7% complete responses. Seventy three percent of patients had a duration of response of 6 months or longer.
  - The following patients were excluded from the study: Patients with endometrial sarcoma and patients who had prior therapy with a PD-1/PD-L1 inhibitor.
- Subsequently, Jemperli (dostarlimab) was evaluated in a large, randomized, double-blind, placebo-controlled trial (RUBY study) as part of a front-line regimen for patients with advanced endometrial cancer for tumors that are dMMR or microsatellite instability-high (MSI-H). [4]
  - Patients enrolled in the study had no prior systemic therapy in the advanced disease setting, including no prior PD-1/PD-L1 inhibitor therapy. More specifically, patients included in the study had:
    - Primary advanced stage III or IV disease,
    - Initial recurrent disease without prior systemic therapy, or
    - Recurrent disease previously treated with neoadjuvant or adjuvant systemic therapy with recurrence or progression at least 6 months after completion or treatment (first recurrence).

    * Jemperli (dostarlimab) or placebo was initiated in combination with carboplatin plus paclitaxel chemotherapy for six cycles and was then continued as a single agent until disease progression.
    * The study enrolled patients with both mismatch repair deficient (dMMR) and mismatch repair proficient (pMMR) tumors. Though an initial interim analysis of progression-free survival (PFS) concluded that the any benefit was attributable to the dMMR subgroup, a later analysis of the mature overall survival (OS) endpoint demonstrated a statistically significant and clinically relevant OS advantage that extended to patients with tumor that were MMR proficient (pMMR tumors). [5]
    * The median OS reported in the study was 44.6 months and 28.2 months in the Jemperli (dostarlimab) and placebo treatment arms, respectively (HR 0.69 [95% CI 0.54, 0.89]; p = 0.002).
- The National Comprehensive Cancer Network (NCCN) Uterine Neoplasms guideline lists Jemperli (dostarlimab) as a monotherapy among potential treatment options for progressive/advanced dMMR or MSI-H endometrial carcinoma in the subsequent-line treatment setting. It is also listed among preferred front-line regimens for recurrent disease when used in combination with carboplatin and paclitaxel, regardless of MMR status. [1]

REAUTHORIZATION CRITERIA:

- When coverage criteria are met, Jemperli (dostarlimab) is authorized for six months (24 weeks) of therapy, after which time documentation must be provided to establish that the medication is effective. Specifically, there must be documentation of clinical benefit, including disease stability or improvement and there is a lack of disease progression, based on an assessment of change in tumor burden.
    * The standard of care for evaluation of response to cancer immunotherapy, such as Jemperli (dostarlimab), is use of the iRECIST criteria for assessment of tumor burden. [6]
    * The iRECIST criteria include use of quantitative and qualitative criteria for assessment of change in tumor burden for target lesions and non-target lesions. [7]
        ▪ Quantitative measurements for target lesions (tumor size and % change)
        ▪ Qualitative evaluation for non-target lesions (present/disappeared/ unequivocal progression)
    * Documentation of benefit must include an assessment of the most recent imaging (“restaging scans”) by the treating oncologist. Given the complexity of the evaluation, including use of the iRECIST criteria, Jemperli (dostarlimab) will not be reauthorized without an assessment of response to therapy, such a partial response (iPR), complete response (iCR), or stable disease (iSD).
    * Use of immunotherapy may result in pseudoprogression, due to immune and T-cell activation, which can appear similar to tumor flare. If there is documentation of potential disease progression [“unconfirmed progressive disease (iUPD)”], a shortened authorization (up to three months) may be approved to allow time for

clarification of response to Jemperli (dostarlimab), including clinical re-evaluation of the patient and reimaging. Guidelines recommend reimaging for iUPD after 4-8 weeks.

* If a patient has confirmed, unequivocal new lesions (progression of disease, iPD), additional Jemperli (dostarlimab) is not coverable. If a new lesion is equivocal, iUPD reassessment by the treating oncologist with repeat imaging would apply (as noted above).

INVESTIGATIONAL USES

- Jemperli (dostarlimab) is actively being studied to determine if there is benefit in treating other types of cancers including non-small cell lung cancer and malignant melanoma. [8] To date, studies are preliminary and ongoing and the risk versus potential for clinical benefit remains under investigation.
- ***dMMR Solid Tumors (other than EC)*** [9]
  * Jemperli (dostarlimab) is FDA approved as a treatment option for patients with any progressive dMMR solid tumor ("tumor agnostic") when no satisfactory treatment alternatives are available.
  * The Accelerated approval of Jemperli (dostarlimab) for all dMMR solid tumors was based on preliminary results from a 'basket trial' which included patients with any type of solid tumor as long as it was dMMR. The sample size for most tumors was very small with most tumor types being represented in only one or two patients. Additionally, the population did not include all types of solid tumors.
  * Subjects enrolled in the trial had advanced solid tumors, at least one prior chemotherapy regimen, and no acceptable treatment alternatives.
  * Although reported tumor response rates appear promising, it is not known if Jemperli (dostarlimab) improves tumor response in all dMMR solid tumors, or positively impacts any clinically relevant outcome. Confirmatory studies are necessary to establish clinical benefit. Therefore, the use of Jemperli (dostarlimab) for dMMR tumors (other than EC) is considered investigational.

Dosing [9]

- ***Jemperli (dostarlimab) as part of a front-line regimen for advanced endometrial cancer:*** 500 mg IV every 3 weeks for six doses in combination with carboplatin and paclitaxel, followed by single agent Jemperli (dostarlimab) 1,000 mg IV every six weeks until disease progression.
- ***Jemperli (dostarlimab) as a single agent for advanced endometrial cancer that has progressed on prior chemotherapy:*** 500 mg IV every 3 weeks for four doses, followed by 1000 mg IV every 6 weeks until disease progression.

Safety [9]

- Package labeling warns of the potential for immune-mediated adverse effects and infusion-related reactions.
- The overall safety profile of Jemperli (dostarlimab) appears similar to other PD-1 inhibitors.

Appendix 1: FDA-approved PD-1 and PD-L1 blocking monoclonal antibody therapies [a]
Programmed death receptor-1 (PD-1) inhibitors
Jemperli (dostarlimab)
Keytruda (pembrolizumab)
Libtayo (cemiplimab-rwlc)
Loqtorzi (toripalimab)
Opdivo (nivolumab)
Tevimbra (tislelizumab)
Zynyz (retifanlimab)
Programmed death-ligand 1 (PD-L1) inhibitor
Tecentriq (atezolizumab)
Bavencio (avelumab)
Imfinzi (durvalumab)

[a] Or as listed on the FDA.gov website.

Cross References
Bavencio, avelumab, Medication Policy Manual, Policy No. dru499
Keytruda, pembrolizumab, Medication Policy Manual, Policy No. dru367
Lenvima, lenvatinib, Medication Policy Manual, Policy No. dru398
Opdivo, nivolumab, Medication Policy Manual, Policy No. dru390

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Revision History

Revision Date	Revision Summary
9/19/2024	**Effective 1/1/2025:** • Changed reauthorization from 'may' to 'shall.' Operationally, all approvals will be for 24 weeks (6 months). Ongoing therapy (beyond 24 weeks) will be subject to reauthorization review every 24 weeks, for documentation of disease stability or improvement and lack of disease progression.
9/19/2024	**Effective 12/1/2024:** • Updated criterion II.C.1.a. to read 'No prior systemic therapy for endometrial carcinoma in the advanced treatment setting' (from 'No prior systemic therapy for endometrial carcinoma') to clarify intent (no change to overall intent of coverage criteria). • Removed criterion II.C.1.b to reflect new evidence showing that Jemperli (dostarlimab) also provides benefit in the front-line setting when used with carboplatin and paclitaxel in tumors with pMMR status. *(a new FDA indication expanding use from the population with dMMR tumors to the population with either dMMR OR pMMR tumors)*
12/7/2023	Coverage for Jemperli (dostarlimab) was added for advanced endometrial cancer when used as part of a front-line regimen (no prior systemic therapy) for tumors that are mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) when initiated in combination with carboplatin and paclitaxel and there has been no prior use of PD-1 or PD-L1 inhibitor therapies.
12/9/2022	• Updated standard language in policy. • No changes to coverage criteria with this annual update.
10/15/2021	New policy (effective 11/15/2021). • Limits coverage to patients with progressive/advanced dMMR endometrial cancer after there has been progression on standard of care front-line cytotoxic chemotherapy. • Added use in other dMMR solid tumors (a new indication since the original approval) as investigational because clinical benefit in this expanded, tumor agnostic setting has not been established. • Sequential use of PD-1/PD-L1 inhibitor therapies has not been studied or shown to be effective and is therefore not coverable.

Drug names identified in this policy are the trademarks of their respective owners.

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Medication Policy Manual

Policy No: dru675

Topic: Zynlonta, loncastuximab tesirine-lpyl

Date of Origin: November 15, 2021

Committee Approval Date: March 6, 2025

Next Review Date: 2026

Effective Date: May 1, 2025

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Zynlonta (loncastuximab tesirine-lpyl) is an antibody-drug conjugate that binds to the CD19 antigen on B-lymphocytes and on several B-cell cancers. It is used in the treatment of relapsed or refractory large B-cell lymphoma where disease has progressed after at least two prior therapies.

Policy/Criteria

Most contracts require pre-authorization approval of Zynlonta (loncastuximab tesirine-lpyl) prior to coverage.

I. Continuation of therapy (COT): Zynlonta (loncastuximab tesirine-lpyl) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

II. New starts (treatment-naïve patients): Zynlonta (loncastuximab tesirine-lpyl) may be considered medically necessary when criteria A through D below are met.

A. A diagnosis of one of the following types of **relapsed or refractory large B-cell lymphoma**:

1. Diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS).

2. DLBCL arising from low-grade lymphoma.

3. High-grade B-cell lymphoma.

AND

B. There was disease progression on or after at least two prior systemic lymphoma therapies.

AND

C. Zynlonta (loncastuximab tesirine-lpyl) will be used as monotherapy.

AND

D. There has been no prior use of Zynlonta (loncastuximab tesirine-lpyl).

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Zynlonta (loncastuximab tesirine-lpyl) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Zynlonta (loncastuximab tesirine-lpyl) will be authorized as follows:

1. ***Initial two cycles:*** Doses up to 150 mcg/kg for up to two infusions in six weeks.
2. ***Subsequent cycles:*** Doses up to 75 mcg/kg for up to one infusion every three weeks until disease progression.

C. Authorization **may** be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, including disease stability or improvement, relative to baseline symptoms.

IV. Zynlonta (loncastuximab tesirine-lpyl) is considered investigational when used for all other conditions, unless otherwise specified in the coverage criteria above.

Position Statement

Summary

- Zynlonta (loncastuximab tesirine-lpyl) is a CD19-directed antibody-drug conjugate approved for use in patients with relapsed or refractory (R/R) large B-cell lymphoma, including diffuse large B-cell lymphoma not otherwise specified (DLBCL NOS), DLBCL arising from low-grade lymphoma, and high-grade B-cell lymphoma, after two or more lines of systemic therapy.
- The intent of this policy is to allow coverage of Zynlonta (loncastuximab tesirine-lpyl) in the setting described above (in the coverage criteria), where it has been evaluated for efficacy, up to the dose shown to be safe in clinical trials. The FDA approval was based on low-quality data from a single, small, non-comparative, non-blinded study that evaluated an endpoint that has not been proven to predict clinical benefit.
- Zynlonta (loncastuximab tesirine-lpyl) was evaluated in patients with relapsed or refractory DLBCL, NOS. The population included patients with transformed disease, as well as a small population of patients with high-grade lymphoma. All patients enrolled in the study had at least two prior systemic therapies for their lymphoma.
- The efficacy of Zynlonta (loncastuximab tesirine-lpyl) relative to other salvage therapies used for DLBCL is not known as head-to-head studies have not been conducted.
- Repeat use of Zynlonta (loncastuximab tesirine-lpyl) after disease progression has not been studied and is considered investigational. Based on its mechanism of action, there is the potential that it might impact the efficacy of subsequent therapies that bind to CD19, such as CAR T-cell therapies. Further study is warranted.
- The National Comprehensive Cancer Network (NCCN) B-cell lymphomas guideline lists Zynlonta (loncastuximab tesirine-lpyl) among options for DLBCL that has progressed on

or after at least two prior therapies.

- Zynlonta (loncastuximab tesirine-lpyl) is given as a 30-minute infusion in a dose of 150 mcg/kg IV every three weeks for two cycles. The dose is then decreased to 75 mcg/kg IV every three weeks until disease progression.
- The safety and effectiveness of Zynlonta (loncastuximab tesirine-lpyl) in conditions other than advanced DLBCL have not been established.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy [1,2]

- The efficacy of Zynlonta (loncastuximab tesirine-lpyl) was evaluated in a small, non-comparative, non-blinded study that evaluated tumor response as an endpoint. The quality of this data is poor due to the lack of randomization, blinding, and comparator. Furthermore, tumor response is not predictive of improvement in any clinically relevant outcome (e.g., improved survival or quality of life).
    * The study evaluated patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) whose disease had progressed on or after at least two prior multi-agent systemic treatment regimens.
    * The majority of the population (127/145; 88%) had a diagnosis of DLBCL, not otherwise specified (NOS). There was also a small population (11/145; 8%) of patients in the trial with high-grade B-cell lymphoma. Twenty percent of the population had transformed DLBCL.
    * One percent of the study population had a prior allogeneic stem cell transplant (SCT), 14% of the population had a prior autologous SCT, and 9% of the

population had prior CAR T-cell therapy.

* Study exclusions:
  - Patients with CNS lymphoma.
  - Patients with bulky disease (tumors ≥ 10 cm) were excluded in a protocol amendment after it was found they had a poor response to this therapy.

- It is not known how the efficacy of Zynlonta (loncastuximab tesirine-lpyl) compares with any other therapy for DLBCL as no head-to-head studies have been conducted.
- The National Comprehensive Cancer Network (NCCN) B-cell lymphomas guideline lists Zynlonta (loncastuximab tesirine-lpyl) among potential treatment options for relapsed or refractory DLBCL when disease has progressed on or after at least two prior systemic therapies. [3]

Investigational Uses [4]

- There are currently no published clinical trials evaluating the safety or efficacy of Zynlonta (loncastuximab tesirine-lpyl) for the treatment of conditions other than the large B-cell lymphoma subtypes listed in the coverage criteria.
- There are future studies planned that will evaluate the use of Zynlonta (loncastuximab tesirine-lpyl) in other B-cell lymphomas and in specific non-Hodgkin lymphomas.

Safety and Tolerability [5]

- Approximately one-quarter of the patients enrolled in the Zynlonta (loncastuximab tesirine-lpyl) clinical trial discontinued therapy due to an adverse event (AE). Fifty-one percent of patients required an interruption in treatment due to an AE.
- There is a theoretical potential that Zynlonta (loncastuximab tesirine-lpyl), as well as other CD19-directed lymphoma therapies, might negatively impact the efficacy of subsequent anti-CD19 CAR T-cell therapies.

Appendix 1: DLBCL, not otherwise specified (NOS)
• Defined in the World Health Organization (WHO) classification of mature lymphoid neoplasms • Diagnosis of exclusion • ICD10 codes(s): C83.30 to C83.39, depending on site of tumor

Cross References
Bispecific T-cell Engager (BiTE) Therapies for B-cell Lymphoma, Medication Policy Manual, Policy No. dru761
Chimeric Antigen Receptor (CAR) T-cell Therapies, Medication Policy Manual, Policy No. dru523
Monjuvi, tafasitamab, Medication Policy Manual, Policy No. dru652
Products with Therapeutically Equivalent Biosimilars/Reference Products, Medication Policy Manual, Policy No. dru620
Polivy, polatuzumab vedotin, Medication Policy Manual, Policy No. dru600
Xpovio, selinexor, Medication Policy Manual, Policy No. dru607

Codes	Number	Description
HCPCS	J9359	Injection, loncastuximab tesirine-lpyl (Zynlonta), 0.1 mg

References

1. Caimi PF, Ai W, Alderuccio JP, et al. Loncastuximab tesirine in relapsed or refractory diffuse large B-cell lymphoma (LOTIS-2): a multicentre, open-label, single-arm, phase 2 trial. *Lancet Oncol.* 2021;22(6):790-800. PMID: 33989558
2. Center for Drug Evaluation and Research; U.S. Food and Drug Administration Multi-Disciplinary Review & Evaluation BLA 761-196; loncastuximab tesirine-lpyl (Zynlonta™). [cited 6/30/2021]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/761196Orig1s000MultidisciplineR.pdf.
3. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. [Updated routinely]. [cited with policy updates and as necessary]. Available from: https://www.nccn.org/guidelines/category_1.
4. National Institutes of Health, Clinicaltrials.gov [website]. [cited periodically]. Available from: www.clinicaltrials.gov.
5. Zynlonta (loncastuximab tesirine-lpyl) [package insert]. ADC Therapeutics America; Murray Hill, NJ; October 2022.

Revision History

Revision Date	Revision Summary
3/6/2025	No changes to coverage criteria with this annual review.
3/21/2024	No criteria changes with this annual review.
3/16/2023	No changes to coverage criteria with this annual update.
3/18/2022	• No changes to coverage criteria with this annual update • Policy language updated so standard template language (no change to intent).
10/15/2021	New policy (effective 11/15/2021). • Limits coverage of Zynlonta (loncastuximab tesirine-lpyl) as a monotherapy in patients with relapsed or refractory DLBCL NOS, DLBCL arising from low-grade lymphoma, and high-grade B-cell lymphoma when disease has progressed on or after at least two prior systemic lymphoma therapies. Sequential use of Zynlonta (loncastuximab tesirine-lpyl) has not been studied or shown to be effective and is therefore not coverable.

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Medication Policy Manual

Policy No: dru677

Topic: Interleukin-1 Antagonists

- Arcalyst, rilonacept
- Ilaris, canakinumab
- Kineret, anakinra

Date of Origin: October 1, 2021

Committee Approval Date: June 20, 2024

Next Review Date: 2025

Effective Date: October 1, 2024

IMPORTANT REMINDER

This Medical Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medical policy is to provide a guide to coverage. Medical Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Arcalyst (rilonacept), Ilaris (canakinumab), and Kineret (anakinra) are medications that block the activity of interleukin-1 (IL-1), a protein involved in inflammation.

Policy/Criteria

Most contracts require pre-authorization approval of interleukin-1 antagonists prior to coverage.

I. Continuation of therapy (COT): Interleukin-1 antagonists, Arcalyst (rilonacept), Ilaris (canakinumab), and Kineret (anakinra), may be considered medically necessary for COT when criterion A **AND** B below are met.

A. One of the following (1, 2, or 3):

1. For diagnoses NOT listed in the coverage criteria below, criteria a through c below must be met:

a. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

b. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

AND

c. Step therapy with prior use of lower cost interleukin-1 antagonists is met (i or ii):

i. For Arcalyst (rilonacept) only (1 or 2):

1. There is documentation of prior treatment with Kineret (anakinra), and treatment was ineffective or not tolerated, unless use is documented as medically contraindicated.

OR

2. The prescriber has submitted clinical rationale that establishes Kineret (anakinra) is not a treatment option. The rationale is supported by known clinical characteristics of the patient as well as clinical properties of Kineret (anakinra).

OR

ii. For Ilaris (canakinumab) only (1 or 2):

1. There is documentation of prior treatment with Arcalyst (rilonacept) and Kineret (anakinra), and each was ineffective or not tolerated, unless use is documented as medically contraindicated.

OR

2. The prescriber has submitted clinical rationale that establishes Arcalyst (rilonacept) and Kineret (anakinra) are BOTH not a treatment option. The rationale is supported by known clinical

characteristics of the patient as well as clinical properties of BOTH Arcalyst (rilonacept) and Kineret (anakinra).

PLEASE NOTE: *Documentation of prior use of and response to lower-cost therapy, including use in the distant past, must be provided for this criterion to be met.*

OR

2. For diagnoses listed in the coverage criteria below, criteria a, b, and c must be met:

a. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

b. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

AND

c. Step therapy with lower cost interleukin-1 antagonists is met (i or ii):

i. ***For Arcalyst (rilonacept) ONLY*:** There is documentation of prior treatment with Kineret (anakinra), and treatment was ineffective or not tolerated, unless use is documented as medically contraindicated.

OR

ii. ***For Ilaris (canakinumab) ONLY*:** There is documentation of prior treatment with Arcalyst (rilonacept) **AND** Kineret (anakinra), and each was ineffective or not tolerated, unless use is documented as medically contraindicated.

OR

3. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

AND

B. **For Ilaris (canakinumab) ONLY:** Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, Site of Care Review, dru408].

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Interleukin-1 antagonists may be considered medically necessary in patients when one of the diagnostic criterion A through E **AND** F below are met.

A. Recurrent pericarditis (RP)

Arcalyst (rilonacept) and Kineret (anakinra) may be considered medically necessary for RP when there is clinical documentation (including, but not limited to chart notes) that criteria 1 through 3 below are met:

1. A diagnosis of RP established by or in conjunction with a specialist in cardiology, rheumatology, or immunology.

AND

2. The patient has had an episode of recurrent pericarditis while currently taking colchicine. If colchicine is contraindicated or not tolerated, low-dose corticosteroids must have been ineffective, contraindicated, or not tolerated.

AND

3. **For Arcalyst (rilonacept) only:** Prior treatment with Kineret (anakinra) was ineffective, unless not tolerated or use is contraindicated.

OR

B. Rheumatoid arthritis (RA)

Kineret (anakinra) may be considered medically necessary for RA when criteria 1 through 3 below are met:

1. A diagnosis of RA when established by or in consultation with a specialist in rheumatology.

AND

2. Treatment with a conventional synthetic DMARD (csDMARD) for at least 6 to 12 weeks was ineffective, not tolerated, or all csDMARDs are contraindicated. csDMARDs for RA include hydroxychloroquine, leflunomide, methotrexate, and sulfasalazine.

AND

3. There is clinical documentation that treatment with **at least two** Level 1 or Level 2 self-administered therapies was not effective after at least a 12-week treatment course unless all were not tolerated or are contraindicated.

Level 1 or 2 Treatments for Rheumatoid Arthritis	
Level 1	• Enbrel (etanercept) • Humira (adalimumab)
Level 2	• Rinvoq (upadacitinib) • Xeljanz/Xeljanz XR (tofacitinib)

OR

C. Still's disease [systemic juvenile idiopathic arthritis (SJIA) or adult-onset still's disease (AOSD)]

Ilaris (canakinumab) and Kineret (anakinra) may be considered medically necessary for Still's disease (SJIA and AOSD) when there is clinical documentation (including, but not limited to chart notes) that criteria 1 through 4 below are met:

1. A diagnosis of Still's disease (SJIA; AOSD) when established by or in consultation with a specialist in rheumatology.

AND

2. There is disease activity greater than 6 weeks.

AND

3. One of the following are met:

a. Treatment with at least one oral conventional synthetic DMARD (csDMARD) was not effective after 12 weeks, not tolerated, or is contraindicated. csDMARDs for the treatment of SJIA include azathioprine, cyclosporine, leflunomide, methotrexate, systemic corticosteroids, and tacrolimus.

b. Treatment with at least one NSAID (e.g., ibuprofen, celecoxib) was not effective after 4 weeks, not tolerated, or all are contraindicated.

AND

4. **For Ilaris (canakinumab) only:** Prior treatment with both Actemra (tocilizumab) and Kineret (anakinra) has been ineffective, not tolerated or is contraindicated.

OR

D. Periodic fever syndromes

Arcalyst (rilonacept), Ilaris (canakinumab), and Kineret (anakinra) may be considered medically necessary for periodic fever syndromes when there is clinical documentation (including, but not limited to chart notes) that criteria 1 and 2 below are met:

1. **For Arcalyst (rilonacept) and Ilaris (canakinumab) only:** Prior treatment with Kineret (anakinra) was ineffective, unless not tolerated or use is contraindicated.

AND

2. One of the following diagnostic criterion (a through d) below is met AND established by or in consultation with a specialist in rheumatology, immunology, or hematology:

a. A diagnosis of **cryopyrin associated periodic syndromes (CAPS)** and criteria i, ii, and iii below are met:

i. There is laboratory evidence of a genetic mutation in the cold-induced auto-inflammatory syndrome 1 (CIAS1 – sometimes referred to as the NLRP3).

AND

ii. There is clinical documentation of at least one of the following types of CAPS (1, 2, or 3) below:

1. **Neonatal onset multisystem inflammatory disease (NOMID)**.

OR

2. **Familial cold auto-inflammatory syndrome (FCAS)**.

OR

3. **Muckle-Wells syndrome (MWS)**.

AND

iii. **For Arcalyst (rilonacept) and Ilaris (canakinumab) only:** Documented significant functional impairment as a result of CAPS, leading to limitations in activities of daily living (ADLs).

OR

b. A diagnosis of **Familial Mediterranean fever (FMF)** and treatment with colchicine was ineffective, not tolerated, or is contraindicated.

OR

c. A diagnosis of **Tumor necrosis factor receptor-1 associated periodic syndrome (TRAPS)**, as confirmed by genetic testing.

OR

d. A diagnosis of **Hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD)**, as confirmed by elevated immunoglobulin D (IgD) levels and/or genetic testing.

OR

E. **Deficiency of interleukin-1 receptor antagonist (DIRA)**

Arcalyst (rilonacept) and Kineret (anakinra) may be considered medically necessary for DIRA when there is clinical documentation (including, but not limited to chart notes) that criteria 1 and 2 below are met:

1. A diagnosis of DIRA established by or in conjunction with a specialist in rheumatology, or immunology.

AND

2. **For Arcalyst (rilonacept) only:** Prior treatment with Kineret (anakinra) was ineffective, not tolerated, or is contraindicated.

AND

F. **For Ilaris (canakinumab) ONLY:** Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, Site of Care Review, dru408].

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Arcalyst (rilonacept) and Kineret (anakinra) coverable only under the pharmacy benefit (as self-administered medications).

B. Regence Pharmacy Services considers Ilaris (canakinumab) coverable only under the medical benefit (as a provider-administered medication).

C. When pre-authorization is approved, interleukin-1 antagonists will be authorized in quantities as listed in Table 1:

TABLE 1.

Product	Quantity Limit
Arcalyst (rilonacept)	**1. For periodic fever syndromes and RP:** **a.** Initial: Up to 25 vials containing 220 mg each in the first 24-week period (based on a loading dose of 320 mg once followed by 160 mg weekly). **b.** Continued Authorization: Up to four 220 mg vials per 28 days (based on a dose of 160 mg every week). **2. For DIRA:** Up to 320 mg (2 vials) per week.
Ilaris (canakinumab)	**1. For CAPS:** Up to 1 vial (150 mg) every 8 weeks (i.e., 7 vials in a 12-month period). **2. For FMF, TRAPS, HIDS/MKD:** Up to 2 vials (300 mg) every 4 weeks (i.e., 26 vials in a 12-month period). **3. For SJIA and AOSD:** Up to 2 vials (300 mg) every 4 weeks (i.e., 26 vials in a 12- month period).
Kineret (anakinra)	**1. For RA, RP, SJIA, AOSD, FMF, TRAPS, HIDS/MKD:** Up to 28 doses (twenty-eight 100 mg syringes) every 4 weeks. **2. For CAPS and DIRA:** A quantity sufficient for up to 28 doses every four weeks based on a recommended maximum dose of 8 mg/kg per day.

AOSD: Adult-onset still's disease; CAPS: cryopyrin associated periodic syndromes; DIRA: deficiency of interleukin-1 receptor antagonist; FMF: Familial Mediterranean fever; HIDS: Hyperimmunoglobulin D syndrome; MKD: mevalonate kinase deficiency; RA: rheumatoid arthritis; RP: recurrent pericarditis; SJIA: systemic juvenile idiopathic arthritis; TRAPS: tumor necrosis factor receptor-1 associated periodic syndrome.

C. Authorization Limits:

TABLE 2.

Product	Authorization Limit
Arcalyst (rilonacept)	**1. For Periodic fever syndromes:** **a.** Initial authorization: **Shall** be reviewed at 6 months. **b.** Continued authorization: **Shall** be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement of associated symptoms. **2. For RP and DIRA:** Authorization **may** be reviewed at least annually to confirm that current medical necessity criteria are met, and that the medication is effective.
Ilaris (canakinumab)	Initial authorization: **Shall** be reviewed at 6 months. Continued authorization: **Shall** be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement of associated symptoms.
Kineret (anakinra)	Authorization **may** be reviewed at least annually to confirm that current medical necessity criteria are met, and that the medication is effective.

RP: recurrent pericarditis; DIRA: deficiency of interleukin-1 receptor antagonist.

IV. Interleukin-1 antagonists are considered investigational when used for all other conditions including, but not limited to:

A. Atherosclerotic coronary artery disease (ASCAD).

B. Bursitis.

C. Chronic Kidney Disease (CKD).

D. Diabetes Mellitus Type 1 (DM).

E. Gout.

Position Statement

Summary

- Arcalyst (rilonacept), Ilaris (canakinumab), and Kineret (anakinra) are interleukin-1 antagonists) used in the treatment of several inflammatory conditions.
- The intent of this policy is to cover interleukin-1 (IL-1) antagonists for the indications and dose for which they have been shown to be safe and effective in the available evidence, as detailed in the coverage criteria.
- Other than rheumatoid arthritis (RA), there is limited overall evidence for the use of IL-1 antagonists given the rarity of most of the conditions for which IL-1 antagonists are used. Much of the evidence is of very low quality.
- The general approach to conditions covered in this policy is use of stepwise treatment with various anti-inflammatories, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and colchicine (diagnosis-dependent), as well as use of preferred treatment options. IL-1 antagonists are generally reserved for patients not responding to standard of care.
- There are no head-to-head trials comparing any of the IL-1 antagonists to each other or any other medication in the management of any condition. In several of the covered conditions, lowest-cost Kineret (anakinra) is a treatment option based on years of clinical experience as the first-available IL-1 antagonist.
- For this health plan, Kineret (anakinra) provides the best value among IL-1 antagonists for many of the covered conditions. Therefore, higher-cost IL-1 antagonists [Arcalyst (rilonacept) and Ilaris (canakinumab)] are coverable only when lower-cost Kineret (anakinra) therapy is ineffective or not a treatment option, as detailed in the coverage criteria.
- For patients established on higher-cost IL-1 antagonists [Arcalyst (rilonacept) and Ilaris (canakinumab)] prior to membership with this health plan, continuation of therapy (COT) criteria must be met, including prior use of lower-cost Kineret (anakinra) therapy, unless there is specific documentation that the patient is not a candidate for treatment with Kineret (anakinra).

Clinical Efficacy

Recurrent Pericarditis (RP)

- *Disease background*: [1] RP is characterized by chest pain associated often with peculiar electrocardiographic changes and may be accompanied by pericardial effusion. Pericarditis is considered recurrent (RP) when there has been a recurrence at least 4-6 weeks after the first episode. NSAIDs and colchicine are first-line options to treat pericarditis and prevent recurrences. Guidelines recommend colchicine be continued for at least 6 months. Arcalyst (rilonacept) and Kineret (anakinra) are considered third-line options in patients who have had recurrences despite treatment with colchicine.
- Efficacy of Arcalyst (rilonacept) in recurrent pericarditis (RP) is based on one phase 3 randomized withdrawal study (RHAPSODY). [2 3]
    * Patients with RP were initially assigned to receive Arcalyst (rilonacept) for 16 weeks. Patients who had a response during the initial period were then randomized to continue Arcalyst (rilonacept) (n=30) or switch to placebo (n=31).

    * The primary endpoint was time to first pericarditis recurrence. This was an event driven study, and the study was stopped when 22 events occurred.
    * Results showed that, rilonacept significantly reduced the recurrence of pericarditis compared to patients who were randomized to placebo.
- Efficacy of Kineret (anakinra) is based on one phase 2 randomized-withdrawal trial (AIRTRIP). [4]
    * Kineret (anakinra) was administered at 2 mg/kg per day (up to 100 mg), for 2 months to patients with an episode of pericarditis. Patients who responded to treatment were then randomized to continue Kineret (anakinra) (n = 11) or switch to placebo (n = 10) for 6 months or until an episode of RP occurred.
    * RP occurred in 9 of 10 patients assigned to placebo and 2 of 11 patients assigned to Kineret (anakinra), a significant difference.
    * While the evidence is of lower quality due to the small nature of the study, Kineret (anakinra) does appear to be an effective option for the management of RP.
- 2020 American College of Cardiology Foundation (ACCF) Guidelines for RP list IL-1 blockers as a treatment option for RP; however, no product preference is given. [5]
- 2015 European Society of Cardiology (ESC) Guidelines for pericarditis recommend that aspirin or NSAIDs in combination with colchicine are used as the initial treatment for recurrent pericarditis. Each treatment is then maintained for weeks to months. [1]
    * Low-dose corticosteroids are recommended as second-line agent in patients who cannot tolerate or have a contraindication to colchicine.
    * IVIG, Kineret (anakinra), or azathioprine may be considered in cases of proven-infection negative, corticosteroid-dependent RP not responsive to colchicine. Guidelines have not been updated to include Arcalyst (rilonacept) (2015).
    * After obtaining a complete response, tapering should be done with a single class of drug at a time before colchicine is gradually discontinued.

Rheumatoid Arthritis (RA)

- Several targeted DMARDs, including Kineret (anakinra), have been shown to be effective in the treatment of RA. [6]
- The efficacy of these targeted DMARDs in the treatment of RA is similar. Refer to Drugs for Chronic Inflammatory Diseases, Medication Policy Manual, Policy No. dru444.
- Because of similar efficacy among the studied targeted DMARDs, non-preferred/non-formulary options are coverable when preferred/formulary options are ineffective, as detailed in the coverage criteria.

Systemic Juvenile Idiopathic Arthritis (SJIA; Stills Disease) and Adult- Onset Still's Disease (AOSD):

- *Disease Background:* Systemic JIA is a subtype of juvenile idiopathic arthritis that is associated with systemic inflammation, [7] such as erythematous rash, lymphadenopathy, hepatomegaly or splenomegaly, and serositis.
- IL-6 inhibitor Actemra (tocilizumab) and IL-1 antagonists [Ilaris (canakinumab) and Kineret (anakinra) only] are shown to improve signs and symptoms of SJIA, as

measured by the adapted JIA American College of Rheumatology (ACR) 30 response. Specifically, the evidence is as follows:

* The efficacy of Ilaris (canakinumab) for SJIA was based on two randomized placebo-controlled trials. [8] The primary endpoints included JIA ACR 30 response in Study 1 (n=84) and time to disease flare in Study 2 (n=177, 71 of whom were responders rolled over from Study 1). The majority of patients included in clinical trials of Ilaris (canakinumab) for SJIA were receiving methotrexate and prednisone at the time of study enrollment, and > 50% of patients had prior treatment with a biologic [e.g., Actemra (tocilizumab), Kineret (anakinra), anti-TNF agents or other biologics].
* The efficacy of Actemra (tocilizumab) and Kineret (anakinra) in SJIA was based on one RCT for each, with an improvement in ACR30, with an odds ratio favoring the biologic therapy over placebo. [9]
* At this time, the use of Arcalyst (rilonacept) for SJIA is considered investigational. Arcalyst (rilonacept) was studied in 24 systemic juvenile idiopathic arthritis (SJIA) patients in a double-blind, 4-week trial followed by an open-label phase for 23 months in 23 of these patients. Patients received 2.2 mg/kg or 4.4 mg/kg of Arcalyst (rilonacept). Improvements in clinical and laboratory measures of articular and systemic manifestations of SJIA were achieved in > 50% of Arcalyst (rilonacept)-treated patients over two years. Larger, well-designed trials are needed to establish the efficacy of Arcalyst (rilonacept) in SJIA. [10]

- Consensus guidelines from the Childhood Arthritis Rheumatology and Research Alliance (2012) endorse the use of a step-up treatment of SJIA and include use of Actemra (tocilizumab) and Kineret (anakinra) when biologics are indicated. [11] Updated ACR guidelines (2013) include use of Ilaris (canakinumab) as a biologic option. However, use of Arcalyst (rilonacept) is not recommended. [7]
- The efficacy of the coverable targeted DMARDs (as listed above) in the treatment of SJIA is generally similar. [9 12-14] However, none have been directly compared to each other in a clinical trial and there is a significant difference in the cost between these treatment options. Therefore, the costlier treatment options are coverable only when the less costly options are ineffective. For this health plan, Actemra (tocilizumab) and Kineret (anakinra) provide the best value among biologic medications used to treat SJIA.

Periodic Fever Syndromes - *including CAPS (NOMID, MWS, FCAS), FMF, TRAPS, and HIDS/MKD*

Cryopyrin-associated periodic syndromes (CAPS) – NOMID, MWS, FCAS

- *Disease Background: [15 16]*
  * CAPS are a group of rare genetic diseases affecting approximately 200 to 300 people in the United States, attributed to a specific genetic mutation.
  * Three types of CAPS affect the majority of patients:
    - Familial Cold Auto-Inflammatory Syndrome (FCAS)
    - Muckle-Wells Syndrome (MWS)

    - Neonatal-Onset Multisystem Inflammatory Disease (NOMID)
  * FCAS symptoms include recurrent intermittent episodes of fever and rash that primarily followed natural, artificial (e.g., air conditioning), or both types of generalized cold exposure.
  * MWS symptoms include a syndrome of chronic fever and rash that may wax and wane in intensity and is sometimes exacerbated by generalized cold exposure. This syndrome may be associated with deafness or amyloidosis.
  * NOMID symptoms include urticaria-like rash, CNS involvement [papilledema, cerebrospinal fluid (CSF) pleocytosis, or sensorineural hearing loss], elevated C-reactive protein (CRP), or epiphyseal and/or patellar overgrowth on radiographs.
- Medications that affect interleukin-1 (IL-1) may be helpful in controlling the symptoms of CAPS (NOMID, MWS, FCAS), including Arcalyst (rilonacept), Ilaris (canakinumab), and Kineret (anakinra). However, due to the rarity of these conditions, it has been difficult to conduct high quality scientific studies.
- There is currently insufficient evidence that IL-1 antagonists are efficacious in patients with CAPS (NOMID, MWS, FCAS) who do not exhibit the NLRP3 (CIAS1) genetic mutation.
- There have been no head-to-head trials comparing the efficacy of IL-1 antagonists against each other or any other medication in the management of CAPS (NOMID, MWS, FCAS).
- Kineret (anakinra) is FDA-approved only for NOMID. Arcalyst (rilonacept) and Ilaris (canakinumab) have FDA marketing approval for CAPS, "including MWS and FCAS." However, many patients in the pivotal trials for the FDA approval for Arcalyst (rilonacept) and Ilaris (canakinumab) were previously treated with Kineret (anakinra) for MWS or FCAS, there is years of experience with Kineret (anakinra) based on lower level evidence and use of Kineret (anakinra) is recognized in guidelines, such that Kineret (anakinra) is a potential lower-cost treatment option for patients needing IL-1 antagonists.
- *Evidence for CAPS (MWS or FCAS):*
  * Kineret (anakinra): The evidence for efficacy of Kineret (anakinra) for CAPS (FCAS or MWS) is based on retrospective and observational case series and years of experience. A 2020 comprehensive systematic review of the available evidence for the use of IL-1 antagonists in CAPS reported frequent use of Kineret (anakinra) for CAPS (both MWS and FCAS).[17] In addition, the review noted a number of trials of Ilaris (canakinumab) were in patients with CAPS (MWS, FCAS) previously on Kineret (anakinra). The most common rationale for switching IL-1 antagonist therapy were patient/parent convenience and/or injection site reaction, as well as efficacy. Guidelines recommend Kineret (anakinra) as one of the IL-1 antagonist treatment options for MWS and FCAS.[18]
  * Arcalyst (rilonacept): The evidence for efficacy of Arcalyst (rilonacept) for CAPS (FCAS or MWS) is based on one randomized, crossover study in 47 patients, all positive for the CIAS1 mutation. Patients receiving Arcalyst (rilonacept)

experienced greater clinically meaningful reductions in mean composite symptom scores (about 2 points on a 10-point scale) and maintained improvements compared to placebo after treatment for 24 weeks. [12 19 20]

- Patients initially received 6 weeks of treatment with either Arcalyst (rilonacept) or placebo then were crossed over to the other treatment in a blinded manner.
- At 6 weeks, the symptom scores of patients assigned to Arcalyst (rilonacept) had improved by 2.3 points (on a 10-point scale) relative to patients receiving placebo.
- This modest benefit was sustained for up to 24 weeks of treatment during the clinical trial. A similar benefit (compared to baseline) was seen when patients continued treatment through an open-label extension up to 48 weeks.
- Subjects withdrawn from Arcalyst (rilonacept) following Part A of the trial had a return of symptoms, while those continuing on Arcalyst (rilonacept) maintained their response to treatment.
- Improvement in laboratory test results for inflammatory markers of disease (serum amyloid A and C-reactive protein) were supportive of clinical improvement seen with Arcalyst (rilonacept). These inflammatory markers are not specific to CAPS (i.e., not diagnostic), but might be useful in monitoring clinical response to treatment.

* Ilaris (canakinumab): The evidence for efficacy of Ilaris (canakinumab) for CAPS (FCAS or MWS) is based on one trial (n=35). [21]
  - In phase 1, all patients received a single dose of Ilaris (canakinumab). Those who remained relapse-free after 8 weeks and elected to continue (n=31) were then randomized to receive Ilaris (canakinumab) 150 mg SC every 8 weeks (n=15) or placebo (n=16) for up to 24 weeks.
  - Any patient who relapsed or completed 24 weeks of therapy was then enrolled in an open-label, follow-on trial for at least two doses and up to 52 weeks of therapy.
  - Of the 35 patients initially enrolled, 34 remained relapse-free for 8 weeks.
  - During the double-blinded, randomized phase, all subjects in the Ilaris (canakinumab) group remained relapse-free versus 29% of subjects in placebo group at 24 weeks (100% vs 29%, $p < 0.001$, NNT = 2).
  - Changes in laboratory markers of inflammatory disease (CRP and SAA) were supportive of clinical findings.

- *Evidence for CAPS -neonatal-Onset Multisystem Inflammatory Disease (NOMID):*

* Kineret (anakinra): The efficacy of Kineret (anakinra) for NOMID was based on a prospective, long-term, open-label and uncontrolled study inpatients(n=43) with NOMID aged 0.7 to 46 years who were treated for up to 60 months. [6]
  - Treatment with Kineret (anakinra) resulted in improvements in all individual disease symptoms measured by a disease-specific Diary Symptom Sum Score (DSSS), as well as in the serum markers of inflammation.

- For 11 patients who went through a withdrawal phase, disease symptoms and serum markers of inflammation worsened after withdrawal and promptly responded to reinstitution of Kineret (anakinra) therapy.

* Arcalyst (rilonacept): There is no data for the use of Arcalyst (rilonacept) for NOMID. [17]

* Ilaris (canakinumab): Although trials of Ilaris (canakinumab) for CAPS included patients with NOMID, subsequent data suggests that Ilaris (canakinumab) may be less effective for NOMID as compared to Kineret (anakinra) based on CNS penetration. [22] In addition, a small trial investigated withdrawal of anakinra in patients stable on therapy for NOMID (n=6). After washout, patients were then changed to Ilaris (canakinumab). However, Ilaris (canakinumab) failed to produce a similar response to Kineret (anakinra) and dose escalation was needed.[23] Therefore, Ilaris (canakinumab) is not more effective that Kineret (anakinra), and is significantly more costly. Therefore, Ilaris (canakinumab) is coverable for NOMID only when Kineret (anakinra) is ineffective or not tolerated.

Other Periodic Fever Syndromes: FMF, TRAPS, HIDS/MKD

- *Disease Background: [16 24-26]*

* **Familial Mediterranean Fever (FMF)**
  - The most common periodic syndrome is FMF, which mainly affects people of Eastern Mediterranean ancestry. FMF affects 1 in 250 to 1 in 1,000 individuals in these populations.
  - FMF is characterized by episodic attacks of fever lasting one to three days and accompanied, in most cases, by abdominal pain, pleurisy, and arthralgias/arthritis.
  - Initial treatment of FMF is with colchicine. Colchicine is primarily effective as a prophylactic treatment for FMF attacks.

* **Tumor necrosis factor receptor-1 associated periodic syndrome (TRAPS)**
  - TRAPS is characterized by recurrent fevers over months or years. Other clinical features include focal myalgias, conjunctivitis, and rash. Fever and associated symptoms commonly last at least five days and often continue for more than two weeks.
  - Fever may respond to use of NSAIDs, and glucocorticoids are required to resolve other clinical manifestations of an attack. Off-label treatment with Enbrel (etanercept) for patients with frequent and/or severe recurrences has been reported.
  - The diagnosis of TRAPS is confirmed by genetic testing for disease-associated pathogenic variants in the tumor necrosis factor receptor-1 (TNFR1) gene (TNFRSF1A).

* **Hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD)**
  - HIDS/MKD is characterized by episodic attacks of fever lasting three to

seven days accompanied, in most cases, by chills, cervical lymphadenopathy, abdominal pain, vomiting, and/or diarrhea.

- NSAIDs and glucocorticoids are used to treat the fever and accompanying symptoms. Case reports of treatment with Actemra (tocilizumab), Enbrel (etanercept) and Kineret (anakinra) have been reported in the literature.
- The diagnosis of HIDS/MKD is confirmed by elevated immunoglobulin D (IgD) levels and/or genetic testing.

- Medications that affect interleukin-1 (IL-1) may be helpful in controlling the symptoms of other periodic fevers (FMF, TRAPS, HIDS/MKD) including Arcalyst (rilonacept), Ilaris (canakinumab), and Kineret (anakinra). However, due to the rarity of these conditions, it has been difficult to conduct high quality scientific studies.
- There have been no head-to-head trials comparing the efficacy of IL-1 antagonists against each other or any other medication in the management of other periodic fevers (FMF, TRAPS, HIDS/MKD).
- Only Ilaris (canakinumab) is FDA approved for other periodic fevers (FMF, TRAPS, HIDS/MKD). However, there is years of experience with Kineret (anakinra) based on lower level evidence, and use of Kineret (anakinra) is recognized in guidelines, such that Kineret (anakinra) is a potential lower-cost treatment option for patients needing IL-1 antagonists.
- *Evidence of Efficacy for FMF*
  * Kineret (anakinra): The evidence for efficacy of Kineret (anakinra) for FMF is based on 22 case series and years of experience. [27] In addition, the review noted a number of cases of use of Ilaris (canakinumab) in patients previously on Kineret (anakinra). IL-1 antagonist therapy was switched due to intolerance as well as efficacy.
  * Arcalyst (rilonacept): The evidence for efficacy of Arcalyst (rilonacept) for FMF is based on one small RCT (n=14). However, the complete response rate was low relative to that seen with Ilaris (canakinumab) or Kineret (anakinra). [27 28]
  * Ilaris (canakinumab): The efficacy of Ilaris (canakinumab) for the treatment of FMF, TRAPS, HIDS/MKD was demonstrated in a 4-part study consisting of three separate disease cohorts (FMF, TRAPS, HIDS/MKD). [29] (see "*TRAPS, HIDS/MKD"* below)
- *Evidence of Efficacy for TRAPS, HIDS/MKD:* Due to the rarity of these other periodic fever conditions, available trial evidence is limited.
  * Kineret (anakinra):
    - The evidence for efficacy of Kineret (anakinra) for TRAPS and HIDS/MKD is based on retrospective and observational case series and years of experience. A 2020 comprehensive systematic review of the available evidence for the use of IL-1 antagonists in CAPS reported frequent use of Kineret (anakinra) for TRAPS and HIDS/MKD. [17] In addition, the review noted a number of studies of Ilaris (canakinumab) were in patients with HIDA/MKD previously on Kineret (anakinra). The most common rationale for switching IL-1 antagonist therapy were

patient/parent convenience and/or injection site reaction, as well as efficacy. Guidelines recognize Kineret (anakinra) as one of the IL-1 antagonist treatment options for TRAPS and HIDS/MKD. [18]

* Arcalyst (rilonacept): There is no evidence for the use of Arcalyst (rilonacept) for TRAPS and/or HIDS/MKD. [17]
* Ilaris (canakinumab): The efficacy of Ilaris (canakinumab) for the treatment of FMF, TRAPS, HIDS/MKD was demonstrated in a 4-part study consisting of three separate disease cohorts (FMF, TRAPS, HIDS/MKD). [29]
    - Patients in each cohort entered a 12-week screening period (part 1) during which they were evaluated for the onset of disease flare. Patients aged 2 to 76 years were then randomized at flare onset into a 16-week double-blind, placebo-controlled treatment period (part 2) where they received either 150 mg Ilaris (canakinumab) (2 mg/kg for patients weighing less than or equal to 40 kg) subcutaneously or placebo every 4 weeks.
    - Additional doses of Ilaris (canakinumab) were permitted for patients whose disease flare did not resolve, or who had persistent disease activity. Part 3 and part 4 of the study are ongoing.
    - For the primary efficacy endpoint, Ilaris (canakinumab) was more effective than placebo in the proportion of patients with FMF, TRAPS, and HIDS/MKD who resolved their disease flare at day 15 and had no new flare over the 16 weeks of treatment from the time of resolution of the index flare.

- Guidelines recognize both Ilaris (canakinumab) and Kineret (anakinra) as IL-1 antagonist treatment options for TRAPS and HIDS/MKD. [18] Guidelines for FMF mention use of IL-1 antagonists for colchicine-resistant disease but did not include specific recommendations. [30]
- For this health plan, Kineret (anakinra) provides the best value among IL-1 antagonists used to treat FMF, TRAPS, and HIDS/MKD. Ilaris (canakinumab) was studied in patients previously on Kineret (anakinra) but is not known to be a superior treatment option.

Deficiency of Interleukin-1 Receptor Antagonist (DIRA)

- *Disease Background: [16 31]*
    * DIRA is a rare autoinflammatory disease, caused by loss of function mutations in the IL1RN gene. Prevalence is not known due to the rarity of the condition.
    * It presents with life-threatening systemic inflammation and osteomyelitis with periostitis and pustulosis. Mortality during early infancy is approximately 30%.
    * NSAIDs, conventional immunosuppressants, and steroids are considered only partially effective. Arcalyst (rilonacept) and Kineret (anakinra) are both IL-1 antagonist treatment options.
- *Evidence of Efficacy:* Due to the rarity of the condition, studies are limited to small, single-arm, open-label studies.

* Kineret (anakinra): Efficacy of Kineret (anakinra) for DIRA was based on a single long-term natural history study (n=9) for up to 10 years. After dose adjustment to control active inflammation, all nine patients were able to achieve inflammatory remission.[6 16]
* Arcalyst (rilonacept): Efficacy of Arcalyst (rilonacept) for DIRA was based on a two-year, open-label pilot study in 6 patients with DIRA and responding to Kineret (anakinra) therapy. After switching to Arcalyst (rilonacept), all six patients remained in inflammatory remission for the duration of the 2-year study.[12 31]

- For this health plan, Kineret (anakinra) provides the best value among IL-1 antagonists used to treat DIRA. Arcalyst (rilonacept) was studied in patients previously on Kineret (anakinra) but is not known to be a superior treatment option.

Other Uses

- Gout and gouty arthritis: There is insufficient evidence that use of any IL-1 antagonist is superior to less costly alternatives for gout and/or gouty arthritis, based on preliminary data.
  * A Cochrane systematic review evaluated interleukin-1 antagonists for the treatment of acute gout and concluded that there is low-quality evidence indicated that compared with maximum doses of indomethacin (50 mg three times a day), 320 mg of Arcalyst (rilonacept) may provide less pain relief with a similar rate of adverse events. [32] There is moderate-quality evidence that Ilaris (canakinumab) 150 mg may provide marginal symptomatic relief in people with an acute gout flare compared to a sub-optimal dose of intramuscular triamcinolone.[32 33] However, there is no evidence of that Ilaris (canakinumab) provides any disease modification and a small likelihood that Ilaris (canakinumab) is associated with an increased risk of adverse events. In one clinical trial, Ilaris (canakinumab) was associated with double the rate of overall and serious adverse events relative to triamcinolone.[33] In patients taking Ilaris (canakinumab), after 3 days, the pain level was reduced from 74 to 25 (on a standard rating scale from 0 to 100), whereas in patients taking triamcinolone, the pain level was reduced from 74 to 35. Serious adverse events were 1.4% for Ilaris (canakinumab) versus 0% for triamcinolone. In addition, increased uric acid levels were observed for patients taking Ilaris (canakinumab) versus triamcinolone (44% v 40%, respectively).
  * A phase 2 trial compared Kineret (anakinra) for five days to a single injection of triamcinolone in patients with gout (n=165). Both treatments were similar for gouty flares and associated pain. [34] Clinical guidelines have noted that triamcinolone is considered a weak comparator and there are numerous other treatments available. [35]
  * Arcalyst (rilonacept) was studied in a 16-week, randomized, placebo-controlled study of 241 adult patients with chronic active gouty arthritis who were initiating uric acid-lowering therapy with allopurinol. In addition to allopurinol daily, patients received 16 once-weekly injections of Arcalyst (rilonacept) (80 mg or 160 mg) or placebo. There was a reported improvement in the number of gout

flares per patient through week 16 (primary endpoint) with Arcalyst (rilonacept) vs placebo ($P < 0.001$). [36] However, this data is not helpful to determine the benefit of Arcalyst (rilonacept) relative to less costly alternatives for management of gouty flares, such as NSAIDS or corticosteroids.

- Bursitis: Arcalyst (rilonacept) versus triamcinolone was studied for the treatment of subacromial bursitis in a randomized, non-inferiority, unblinded study. While both treatments improved QuickDASH score, a measure of physical function and pain, triamcinolone offered greater improvement. [37]
- Chronic kidney disease (CKD): Arcalyst (rilonacept) was studied in 39 patients with stage 3 - 4 CKD mineral and bone disorder (CKD-MBD) who completed a randomized trial receiving either the IL-1 trap Arcalyst (rilonacept) (160 mg/week) or placebo for 12 weeks. The following CKD-MBD markers were assessed in serum before and after the intervention: calcium, phosphorus, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, 24,25-dihydroxyvitamin D, intact parathyroid hormone (iPTH), and fibroblast growth factor 23 (FGF23). Results of the trial showed that 12 weeks of IL-1 inhibition did not improve markers of CKD-MBD or physical function.[38]
- Myocardial Infarction (MI): Ilaris (canakinumab) has been studied in patients with previous MI and a high blood level of C-reactive protein.
    * In a phase 3, randomized, placebo-controlled trial, treatment with Ilaris (canakinumab) 150 mg and 300 mg reduced the primary composite endpoint of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death.[39]
    * While promising, additional information is needed to clarify the risk-benefit profile of the drug as the magnitude of benefit is relatively small and Ilaris (canakinumab) had a significantly higher risk of serious infection and sepsis compared to placebo.
- Peripheral artery disease (PAD): One small study evaluated Ilaris (canakinumab) for the treatment of symptomatic peripheral artery disease (PAD). Results showed small improvement in walking distance, however larger, longer-term studies are needed to determine risk-benefit profile and impact on quality of life.[40]
- Other Uses:[41]
    * Ilaris (canakinumab) is also currently being studied in multiple conditions including diabetes mellitus (DM, type 1) and rheumatoid arthritis (RA). Results from these studies are not yet available.
    * Arcalyst (rilonacept) is also currently being studied in multiple other conditions including atherosclerotic coronary artery disease (ASCAD), and diabetes mellitus type 1. Results from these studies are not yet available.

Dosing:

- For FDA labeled uses, the IL-1 antagonists are coverable up to the FDA labeled doses, as studied in the associated clinical trials. [6 12 13]
- For familial Mediterranean fever (FMF), available clinical evidence studied doses of Kineret (anakinra), up to 100 mg per day. [42]
- For other covered uses, studied Kineret (anakinra) dosing was 1-2 mg/kg (up to 5 mg/kg) per day for CAPS (MWS, FCAS), HIDS/MKD and TRAPS. [16 17] Therefore, existing

CAPS (NOMID) Kineret (anakinra) quantity limit of "up to 8 mg/kg/day" is sufficient for treatment of these additional indications.

Cross References
Drugs for chronic inflammatory diseases, Medication Policy Manual, dru444
Products with Therapeutically Equivalent Biosimilars/Reference Products, Medication Policy Manual, dru620
Site of Care Review, Medication Policy Manual, Policy No. dru408

Codes	Number	Description
HCPCS	J0638	Injection, canakinumab (Ilaris), 1 mg

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Revision History

Revision Date	Revision Summary
6/20/2024	Added Ilaris to site of care (SOC) program (effective 10/1/2024).
3/21/2024	• No criteria changes with this annual review. • Ilaris for gout remains investigational despite FDA indication. Background updated to reflect evidence.
3/16/2023	• Clarification of COT criteria (addition of a specific provider rationale). • Clarification of diagnostic criteria for Periodic Fever Syndromes for operational consistency (no change to intent; by a specialist and genetic confirmation for HIDS/MKD and TRAPS). • No change to intent for other indications.
3/18/2022	• Clarification of Continuation of Therapy (COT) criteria, with addition of step therapy with lowest-cost IL-1 antagonist, when possible. • Add step therapy with Kineret (anakinra) for periodic fever syndromes [CAPS (NOMID, MWS, FCAS), FMF, TRAPS, HIDS/MKD] and DIRA, as the lowest-cost IL-1 antagonist, recognized as a treatment option. • Simplification of CAPS criteria for operational purposes. • No change to intent for other indications.
7/16/2021	Effective 10/1/2021: • New combination policy replacing individual policies for Arcalyst, Ilaris, and Kineret (dru159, dru186, and dru444). • For Arcalyst and Kineret, added coverage criteria for recurrent pericarditis and Deficiency of Interleukin-1 Receptor Antagonist (DIRA), newly FDA approved indications. • For Ilaris, and Kineret, added coverage criteria for adult-onset Still's Disease (AOSD), a newly FDA approved indication. • No change to intent for other indications.

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Medication Policy Manual | **Policy No:** dru680

Topic: Evkeeza, evinacumab-dgnb | **Date of Origin:** August 15, 2021

Committee Approval Date: March 16, 2023 | **Next Review Date:** 2024

Effective Date: June 1, 2023

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Evkeeza (evinacumab-dgnb) is an angiopeptin-like 3 (ANGPTL3) inhibitor given intravenously (IV) for the treatment of homozygous familial hypercholesterolemia (HoFH).

Policy/Criteria

Most contracts require pre-authorization approval of Evkeeza (evinacumab-dgnb) prior to coverage.

I. Continuation of therapy (COT): Evkeeza (evinacumab-dgnb) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, full policy criteria must be met for coverage.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Evkeeza (evinacumab-dgnb) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A, B, and C below are met.

A. A diagnosis of **homozygous familial hypercholesterolemia** (HoFH).

AND

B. Evkeeza (evinacumab-dgnb) has been prescribed by or in conjunction with a specialist in cardiology or lipid management and there is clinical documentation of at least one of the following:

1. Genetic confirmation of two mutant alleles at the *LDLR, APOB, PCSK9,* or *LDLRAP1* gene locus.

OR

2. An untreated low-density lipoprotein cholesterol (LDL-C) of > 500 mg/dL (or a treated LDL-C of > 300 mg/dL) with either:

a. Cutaneous or tendon xanthoma before age 10 years.

OR

b. Evidence of heterozygous familial hypercholesterolemia in both parents.

AND

C. Treatment with maximally tolerated statin AND PCSK-9 inhibitor (Repatha [evolocumab] or Praluent [alirocumab]) therapy has been ineffective, contraindicated, or not tolerated.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Evkeeza (evinacumab-dgnb) coverable only under the medical benefit (as a provider-administered medication).

B. When prior authorization is approved, Evkeeza (evinacumab-dgnb) will be authorized in quantities of up to 15 mg/kg once monthly. For doses exceeding 1200 mg, dose rounding down to the nearest available vial size (within 10% of calculated dose) is required.

C. Initial approval shall be up to 6 months. After initial authorization, Evkeeza (evinacumab-dgnb) shall be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as improvement of LDL-C from baseline.

IV. Evkeeza (evinacumab-dgnb) is considered investigational when used for all other indications, including but not limited to:

A. Other causes of hypercholesterolemia, including those with heterozygous familial hypercholesterolemia (HeFH).

B. Prevention of cardiovascular disease (CVD).

Position Statement

Summary

- The intent of this policy is to limit coverage of Evkeeza (evinacumab-dgnb) to patients with a confirmed diagnosis of homozygous familial hypercholesterolemia (HoFH) who have tried and failed lower cost therapies as detailed in the coverage criteria.
- The efficacy and safety of Evkeeza (evinacumab-dgnb) was evaluated in a phase 3, double-blind trial that demonstrated a significant decrease in low density lipoprotein cholesterol (LDL-C) when compared to placebo. Most patients in the study were already established on statin medications prior to study entry. Of note, the effects of Evkeeza (evinacumab-dgnb) on cardiovascular morbidity and mortality have not been determined.
- Treatment guidelines recommend the use of a maximally tolerated high-intensity statin as first-line pharmacotherapy for patients with HoFH, even in patients who are LDL receptor negative, as they have been shown to reduce cardiovascular (CV) and all-cause mortality. [1 2 3] PCSK9 inhibitors are endorsed as add-on therapy for HoFH.[4]

- In addition, statins and PCSK9 inhibitors provide the best value. Evkeeza (evinacumab-dgnb) has not been proven to be safer or more effective than statins or PCSK9 inhibitors but is more costly.
- HoFH may be diagnosed via clinical criteria, such as baseline LDL values, family history, and physical manifestations of FH, or through genetic testing.
- Evkeeza (evinacumab-dgnb) may be covered for up to 15 mg/kg every four weeks, the dose studied in clinical trials. The safety and effectiveness of higher doses have not been established. Dose rounding down to the nearest available vial size may be required within 10% of the calculated dose to reduce product waste without sacrificing efficacy. Dose rounding within 10% of a calculated dose is an accepted industry standard and has been adopted in various clinical care areas.[5]

Background[6 7]

- HoFH is a very rare type of familial hypercholesterolemia (FH), an autosomal dominant lipid disease, that is characterized by abnormally elevated LDL-C levels and an increased propensity for early onset cardiovascular disease.
- Genetic confirmation of two mutant alleles at the *LDLR*, *APOB*, *PCSK9*, or *LDLRAP1* gene locus is confirmative of the presence of HoFH.
- Clinical criteria for FH may be used to guide a clinical diagnosis of HoFH (see *Appendices 1* and *2*).

Clinical Efficacy[8 9 10]

- The efficacy and safety of evinacumab was evaluated in ELIPSE, a phase 3, double-blind, placebo-controlled trial of patients with genetically or clinically confirmed HoFH on stable lipid-lowering therapy.
    * Patients were randomly assigned to an IV infusion of evinacumab 15 mg/kg or placebo every four weeks.
    * 63% of patients were receiving at least three lipid-modifying drugs at baseline; 94% were on a statin and 77% were on a PCSK9 inhibitor.
    * The between group decrease in LDL-C from baseline to week 24 was 49% (absolute change of -132 mg/dL), in favor of Evkeeza (evinacumab-dgnb).
    * The effects of Evkeeza (evinacumab-dgnb) on cardiovascular morbidity and mortality have not been determined.

Investigational Uses

- There are no published clinical trials evaluating the safety or efficacy of Evkeeza (evinacumab-dgnb) for the treatment of other causes of hypercholesterolemia, including those with heterozygous FH (HeFH) and prevention of cardiovascular disease (CVD).

Appendix 1: Dutch Lipid Clinic Network criteria[6]	
Criteria	**Points**
Group 1: family history	
First-degree relative with known premature (less than age 55 for males or 65 for females) coronary heart disease *OR* First-degree relative with known LDL cholesterol above 95th percentile	1
First-degree relative with tendon xanthoma and/or corneal Arcus *OR* Children < 18 years with LDL cholesterol above 95th percentile	2
Group 2: clinical history	
Premature coronary heart disease	2
Subject has cerebral or peripheral vascular disease	1
Group 3: physical examination	
(i) Tendon xanthoma	6
(ii) Corneal arcus in a person before age 45	4
Group 4: biochemical results (LDL-C)	
>8.5 mmol/L (.325 mg/dL)	8
5–8.4 mmol/L (251–325 mg/dL)	5
5.0–6.4 mmol/L (191–250 mg/dL)	3
4.0–4.9 mmol/L (155–190 mg/dL)	1
Group 5: molecular genetic testing (DNA analysis)	
(i) Causative mutation shown in the LDLR, APOB, or PCSK9 genes	8
Scoring	
> 8 points: Definite FH 6-8 points: Probably FH 3-5 points: Possible FH <3 points: Unlikely FH	

Appendix 2: Simon Broome Register Diagnostic Criteria for Definitive FH[7]
Adults: Total cholesterol levels > 290 mg/dL (7.5 mmol/L) or LDL-C > 190 mg/dL (4.9 mmol/L) Children less than 16 years of age: Total cholesterol levels > 260 mg/dL (6.7 mmol/L) or LDL-C > 155 mg/dL (4.0 mmol/L) Plus at least one of the two: **1.** Physical findings: tendon xanthomas or tendon xanthomas in a first or second degree relative. **OR** **2.** DNA-based evidence of an LDL-receptor mutation, familial defective apo B-100, or a PCSK9 mutation.

Cross References
PCSK9 inhibitors, Medication Policy Manual, Policy No. dru697

Codes	**Number**	**Description**
HCPCS	J1305	Injection, evinacumab-dgnb (Evkeeza), 5mg

References

1. Cuchel, M, Bruckert, E, Ginsberg, HN, et al. Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. European heart journal. 2014;35:2146-57. PMID: 25053660.
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3. McGowan MP, Hosseini SH, Moriarty PM, et al. Diagnosis and Treatment of Heterozygous Familial Hypercholesterolemia. J Am Heart Assoc. 2019 Dec 17;8(24):e013225. doi: 10.1161/JAHA.119.013225. Epub 2019 Dec 16. PMID: 31838973.
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9. Vuorio A, Kuoppala J, Kovanen PT, et al. Statins for children with familial hypercholesterolemia. *Cochrane Database of Systematic Reviews.* 2019(11). PMID: CD006401
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Revision History

Revision Date	Revision Summary
3/16/2023	No changes to intent of criteria with this annual update.
3/18/2022	No changes to criteria with this annual update.
7/16/2021	New policy (effective 8/15/2021). Limits coverage to patients with homozygous familial hypercholesterolemia (HoFH) as adjunct to other lipid-lowering therapies, the setting in which it was studied and has a labeled indication.

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Medication Policy Manual | **Policy No:** dru682

Topic: Rybrevant, amivantamab-vmjw | **Date of Origin:** November 15, 2021

Committee Approval Date: September 19, 2024 | **Next Review Date:** 2025

Effective Date: December 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Rybrevant (amivantamab-vmjw) is an intravenously administered medication used in the treatment of advanced or metastatic non-small cell lung cancer (NSCLC).

Policy/Criteria

Most contracts require pre-authorization approval of Rybrevant (amivantamab-vmjw) prior to coverage.

I. Continuation of therapy (COT): Rybrevant (amivantamab-vmjw) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Rybrevant (amivantamab-vmjw) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A and B below are met.

A. A diagnosis of **locally advanced or metastatic non-small cell lung cancer** (NSCLC).

AND

B. Documentation of epidermal growth factor receptor (EGFR) exon 20 insertion mutation and criteria 1 or 2 below are met.

1. First-line: Rybrevant (amivantamab) will be used as part of a front-line regimen (no prior systemic therapy) when used in combination with pemetrexed and platin- based chemotherapy.

OR

2. Subsequent: Rybrevant (amivantamab) will be used as monotherapy when there is disease progression on or after platinum-containing (e.g., carboplatin, cisplatin) chemotherapy regimen unless contraindicated.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Rybrevant (amivantamab-vmjw) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Rybrevant (amivantamab-vmjw) may be approved for up to FDA-recommended dose and frequency limits until disease progression.

C. Authorization **may** be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

IV. Rybrevant (amivantamab-vmjw) is considered not medically necessary when used as subsequent therapy for locally advanced or metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R mutation.

V. Rybrevant (amivantamab-vmjw) is considered investigational when used for all other conditions (including NSCLC without EGFR mutations specified in criteria above) and/or when given concomitantly with any other targeted chemotherapy medication.

Position Statement

Summary

- Rybrevant (amivantamab-vmjw) is an antibody that targets epidermal growth factor receptor (EGFR) and mesenchymal epithelial transition (MET) receptors.
- The intent of this policy is to allow for coverage of Rybrevant (amivantamab-vmjw) for the indication and dose for which it has been shown to be safe and effective, as detailed in the coverage criteria.
- Rybrevant (amivantamab-vmjw) is approved for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with EGFR exon 20 insertion mutations, either as front-line therapy in combination with pemetrexed and carboplatin or as subsequent therapy in those whose disease has progressed on or after platinum-based chemotherapy when given as monotherapy.
- The approval of Rybrevant (amivantamab-vmjw) as subsequent therapy in locally advanced or metastatic NSCLC is based on tumor response rates in a cohort of 81 patients whose tumors had exon 20 insertion mutations. Subsequently, Rybrevant (amivantamab) given with chemotherapy was approved in the first-line setting and found to have a longer progression free survival rate than chemotherapy. In both trials, nearly all patients had adenocarcinoma. The effect of Rybrevant (amivantamab) on clinically meaningful outcomes (such as overall survival) is not known.
- Rybrevant (amivantamab) is considered not medically necessary when given with chemotherapy for locally advanced or metastatic NSCLC with EGFR-Ex19del or L858R after progression with osimertinib. Although there was a marginal two-month progression free survival benefit with combination therapy relative to chemotherapy alone, the addition of Rybrevant (amivantamab) adds significant toxicity in the absence of any proven overall survival benefit.
- The National Comprehensive Cancer Network (NCCN) treatment guideline for NSCLC lists Rybrevant (amivantamab-vmjw) as a treatment option when given as first-line with chemotherapy or as subsequent monotherapy for patients with advanced/metastatic NSCLC with an EGFR exon 20 insertion mutation. Rybrevant (amivantamab) is also listed as an option when given with chemotherapy for locally advanced or metastatic NSCLC with EGFR-Ex19del or L858R after progression with Tagrisso (osimertinib).
- Rybrevant (amivantamab-vmjw) has not been shown to be safe and effective in any other condition or when used in combination with targeted chemotherapy medication.
- There is insufficient evidence to establish the safety or efficacy of the use of Rybrevant (amivantamab) in patients with NSCLC with mutations not specified in this policy. Although the results of the CHRYSALIS trial, using Rybrevant (amivantamab) in patients without biomarker selection are promising, the results are based on the exploratory cohort of the Phase 1, open-label trial. Larger, high-quality randomized controlled clinical trials are needed to establish the dose, clinically meaningful outcomes (such as in overall survival), and safety. As such, the use of Rybrevant in NSCLC for mutations not otherwise specified in this policy is considered investigational.

- Rybrevant (amivantamab-vmjw) may be covered for up to the doses studied in clinical trials, until disease progression or unacceptable toxicity. The safety and effectiveness of higher doses has not been studied.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy [1-3]

The efficacy of Rybrevant (amivantamab-vmjw) for subsequent therapy is based on a low quality, non-comparative, open-label, phase 1 trial in patients with advanced or metastatic NSCLC with an EGFR exon 20 insertion mutation whose disease progressed on or after platinum-based chemotherapy.

- Patients received a median of two prior lines of therapy and either had a performance status of 0 (32%) or 1 (68%). Patients with untreated brain metastasis were excluded. 99% of patients had adenocarcinoma.
- The study evaluated overall response rate (ORR) as the primary endpoint. Tumor response is not a validated surrogate for any clinically relevant endpoint (such as overall survival) in metastatic NSCLC.
- The overall response rate (ORR) was 40%. Most were partial responses (4% were considered complete responses). The duration of response was 11 months.
- The efficacy of Rybrevant (amivantamab-vmjw) relative to other NSCLC therapies (e.g., chemotherapy) is unknown; its place in therapy has not been adequately defined.

Efficacy for Rybrevant (amivantamab) in the front-line setting was evaluated in PAPILLON, a randomized, open-label trial in patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutation. Patients received Rybrevant (amivantamab) in combination with

chemotherapy (carboplatin and pemetrexed) or chemotherapy alone. 99% of patients had adenocarcinoma.

- The primary endpoint was progression-free survival (PFS) as assessed by blinded independent central review (BICR). Rybrevant (amivantamab) plus chemotherapy demonstrated a significant improvement in PFS versus with chemotherapy. The median PFS was 11.4 months and 6.7 months, respectively.
- Although overall survival is not yet mature, preliminary data favors the use of Rybrevant (amivantamab) in combination with chemotherapy.

Rybrevant (amivantamab) was studied in an open-label trial in patients with locally advanced or metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R mutation after progression on Tagrisso (osimertinib). Patients received Rybrevant (amivantamab) plus chemotherapy (carboplatin and pemetrexed) or chemotherapy (carboplatin and pemetrexed) alone.

- Rybrevant (amivantamab)-chemotherapy demonstrated a marginal improvement in progression-free survival (PFS) versus chemotherapy alone (6.3 months and 4.2 months in combination vs chemotherapy alone arms; overall survival is immature. PFS is a surrogate endpoint that has not been correlated with clinical outcomes in this setting.
- Although there was a marginal two-month progression free survival benefit with combination therapy relative to chemotherapy alone, the addition of Rybrevant (amivantamab) adds significant toxicity in the absence of any proven overall survival benefit. Therefore, use of Rybrevant (amivantamab) is considered 'not medically necessary' when given with chemotherapy for locally advanced or metastatic NSCLC with EGFR-Ex19del or L858R after progression with osimertinib, given the lack of superior efficacy and the higher cost versus chemotherapy alone.

Guidelines [4]

- The National Comprehensive Cancer Network (NCCN) NSCLC guideline lists Rybrevant (amivantamab-vmjw) monotherapy as a treatment option for advanced or metastatic disease in the first-line setting when given with chemotherapy or in the subsequent-line setting as monotherapy when an EGFR exon 20 insertion mutation is present. Rybrevant (amivantamab) is also listed as an option when given with chemotherapy for locally advanced or metastatic NSCLC with EGFR-Ex19del or L858R after progression with Tagrisso (osimertinib).
- Chemotherapy has been the standard of care for the subsequent-line treatment of patients with metastatic NSCLC, including patients with EGFR exon 20 insertion mutations, exon 19 deletions or exon 21 L858R mutations.

Investigational Uses

- There are no published clinical trials evaluating the safety or efficacy of Rybrevant (amivantamab-vmjw) outside of the settings above, as described in the coverage criteria.
- The safety and efficacy of Rybrevant (amivantamab-vmjw) have not been established when used in doses higher than listed on the package insert/prescribing information.

Safety [1]

- Overall, the known side effects experienced with Rybrevant (amivantamab-vmjw) appear congruent with EGFR and MET inhibitors and appears be acceptable in a population with metastatic NSCLC. However, approximately 11% of patients in the clinical trial stopped taking Rybrevant (amivantamab-vmjw) due to side effects, suggesting there may be some issues with tolerability.
- When given with chemotherapy, safety is consistent with the known profile of the individual therapy components, but toxicity is additive. In the subsequent setting in patients with either EGFR exon 19 deletion or 21 L858R mutation, grade >3 adverse events (AEs) occurred in 67% and 35% of patients in the Rybrevant (amivantamab)-chemotherapy arm versus chemotherapy arm, respectively; mostly hematologic or dermatologic. Treatment-related serious AEs were reported in 23% of the patients in the Rybrevant (amivantamab)–chemotherapy group and in 9% of those in the chemotherapy group. Four AE related deaths (3%) occurred in the Rybrevant (amivantamab)-chemotherapy arm and three (1%) occurred in the chemotherapy alone arm.[2]
- Infusion-related reactions are also possible. Premedication with diphenhydramine is recommended. For more severe reactions, dexamethasone and acetaminophen may be used.

Codes	Number	Description
HCPCS	J9061	Injection, amivantamab-vmjw (Rybrevant), 2 mg

References

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Revision History

Revision Date	Revision Summary
9/19/2024	• Added coverage for front-line NSCLC with exon 20 insertion mutation in combination with chemotherapy. • Coverage for NSCLC with exon 19 deletion or exon 21 L858R mutation in combination with chemotherapy after progression with Tagrisso (osimertinib) considered not medically necessary. • Use of Rybrevant (amivantamab) for NSCLC without EGFR mutations specified in criteria is considered investigational.
9/14/2023	No criteria changes with this annual review.
9/23/2022	Updated continuation of therapy to allow if established with benefit (standard oncology).
10/15/2021	New policy (effective 11/15/2021). Limits coverage to patients with locally advanced/metastatic NSCLC with EGFR exon 20 insertion mutations as subsequent-line, the setting in which it was studied and has a labeled indication.

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Medication Policy Manual | **Policy No:** dru688

Topic: Saphnelo, anifrolumab | **Date of Origin:** November 15, 2021

Committee Approval Date: March 21, 2024 | **Next Review Date:** 2025

Effective Date: June 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Saphnelo (anifrolumab) is a type I interferon receptor antagonist used for the treatment of patients with systemic lupus erythematosus who are receiving standard therapy.

Policy/Criteria

Most contracts require pre-authorization approval of Saphnelo (anifrolumab) prior to coverage.

I. Continuation of therapy (COT): Saphnelo (anifrolumab) may be considered medically necessary for COT when criterion A, B, or C below **AND** D is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

AND

D. Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, Site of Care Review, dru408].

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Saphnelo (anifrolumab) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A, B, and C below are met.

A. A diagnosis of active, **systemic lupus erythematosus** (SLE) established by or in conjunction with a specialist in rheumatology.

AND

B. Previous treatment with at least one of the following has been ineffective: hydroxychloroquine, methotrexate, azathioprine, or mycophenolate mofetil, unless all are contraindicated or not tolerated.

AND

C. Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, Site of Care Review, dru408].

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Saphnelo (anifrolumab) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Saphnelo (anifrolumab) will be authorized in quantities up to 300 mg every 4 weeks.

C. Authorization may be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, including disease stability or improvement must be provided, relative to baseline symptoms.

IV. Saphnelo (anifrolumab) is considered investigational when used for all other conditions, including but not limited to:

A. Central nervous system lupus.

B. Lupus nephritis.

C. Use in combination with Benlysta (belimumab).

Position Statement

Summary

- Saphnelo (anifrolumab) is an intravenously administered type 1 interferon antagonist approved for the treatment of patients with moderate to severe systemic lupus erythematosus (SLE) who are receiving standard therapy. [1]
- The intent of this policy is to limit use of Saphnelo (anifrolumab) to patients with a diagnosis of SLE who have had inadequate response to standard therapies.
- Saphnelo (anifrolumab) was evaluated in two phase 3 studies and one phase 2 study. All were 52-week double-blind placebo-controlled trials. All patients had disease activity despite treatment with standard SLE therapy (either one or any combination of oral corticosteroids, hydroxychloroquine, and/or immunosuppressants). Results from two of the three studies showed that Saphnelo (anifrolumab) increased the rate of clinical response as measured by validated indices of disease severity. [2 3]
- 2023 European League Against Rheumatism (EULAR) Guidelines for SLE recommend that all patients receive hydroxychloroquine. Immunosuppressants such as methotrexate, azathioprine, or mycophenolate should be considered in patients who had an inadequate response to hydroxychloroquine. Glucocorticoids (e.g., prednisone) are recommended for the treatment of flares and to provide symptom relief. The dose of glucocorticoids should be minimized and withdrawn when possible. [4]

    * Benlysta (belimumab) and Saphnelo (anifrolumab) are recommended in patients with inadequate control to hydroxychloroquine with or without immunosuppressants.

- Saphnelo (anifrolumab) is administered as an intravenous (IV) infusion every 4 weeks. The safety and effectiveness of higher doses have not been established. [1]
- The safety and effectiveness of Saphnelo (anifrolumab) in conditions other than SLE have not been established. Therefore, Saphnelo (anifrolumab) is not recommended in lupus nephritis or central nervous system (CNS) lupus. [1]
- Saphnelo (anifrolumab) has not been studied in combination with other biologic therapies, including Benlysta (belimumab). [1]
- New technologies and pharmaceuticals allow therapeutic services, such as infusion therapy, to be administered safely, effectively, and much less costly outside of hospital-based infusion centers (i.e., hospital outpatient settings). Sites of care such as doctor's offices, infusion centers, home infusion, and approved hospital-based infusion centers are well-established, accepted by physicians, and provide the best value to patients to reduce the overall cost of care.

Clinical Efficacy

- Approval for Saphnelo (anifrolumab) was based on two phase 3 trials and one phase 2 trial. [3] [1]
- All studies were 52-weeks in duration included patients with SLE who were receiving standard therapy (HCQ or immunosuppressive therapy) with or without corticosteroids. Patients were maintained on their existing therapies throughout the trial, except for corticosteroids which were tapered off. [1 3]
- Efficacy was evaluated using Systemic Lupus Erythematosus Responder Index (SRI-4) and BILAG-based Composite Lupus Assessment (BICLA). Both are composite indices of treatment response in SLE though their exact components differ.
- Overall, results showed that treatment with Saphnelo (anifrolumab) increased the rate of response compared to standard therapy alone. However, one phase 3 study (TULIP-1) did not meet its primary endpoint of SRI-4 response.

Investigational Uses

- There are no clinical trials to date supporting the safety or efficacy of Saphnelo (anifrolumab) for the treatment of any condition other than systemic lupus erythematosus.
- The prescribing information for Saphnelo (anifrolumab) contains a limitation of use stating that it has not been evaluated for the treatment of lupus nephritis (LN) or CNS lupus. Although Saphnelo (anifrolumab) is currently being studied in trials for LN, more data is needed to establish safety and efficacy. Use of Saphnelo (anifrolumab) is therefore not recommended in these settings. [1,5]
- Combination use of Benlysta (belimumab) and Saphnelo (anifrolumab) is considered investigational. Clinical trials of Saphnelo (anifrolumab) did not allow combination use. The safety and efficacy of combined use has not been established.

Cross References
Lupkynis, voclosporin, Medication Policy Manual, Policy No. dru678
Site of Care Review, Medication Policy Manual, Policy No. dru408

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Revision History

Revision Date	Revision Summary
3/21/2024	No criteria changes with this annual review.
3/16/2023	No changes to policy criteria with this annual update.
3/18/2022	No changes to policy criteria with this annual update.
11/11/2021	Added SOC requirements to policy to align with dru408 1/1/2022 effective date.
10/15/2021	New policy (effective 11-15-2021). Limits coverage to patients with systemic lupus erythematosus (SLE) in patients with active disease despite standard therapies, the setting in which it was studied and has a labeled indication.

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Medication Policy Manual | **Policy No:** dru690

Topic: Tivdak, tisotumab vedotin | **Date of Origin:** April 15, 2022

Committee Approval Date: December 7, 2023 | **Next Review Date:** 2024

Effective Date: March 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Tivdak (tisotumab vedotin) is an intravenously administered antibody-drug conjugate that is used for treating specific types of cancer (advanced cervical cancer).

Policy/Criteria

Most contracts require pre-authorization approval of Tivdak (tisotumab vedotin) prior to coverage.

I. Continuation of therapy (COT): Tivdak (tisotumab vedotin) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Tivdak (tisotumab vedotin) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A through D below are met.

A. A confirmed diagnosis of **cervical cancer**, recurrent or metastatic.

AND

B. There has been disease progression on or after at least one prior chemotherapy doublet regimen (e.g., cisplatin/paclitaxel, topotecan/paclitaxel).

AND

C. For programmed death-ligand 1 (PD-L1)-expressing tumors with a Combined Positive Score (CPS) $\geq$ 1, there has been disease progression on or after Keytruda (pembrolizumab), unless contraindicated or not tolerated.

AND

D. Tivdak (tisotumab vedotin) will be used as monotherapy.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Tivdak (tisotumab vedotin) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Tivdak (tisotumab vedotin) will be approved for up to FDA-recommended dose and frequency limits until disease progression.

C. Authorization may be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

IV. Tivdak (tisotumab vedotin) is considered investigational when used in the front-line disease setting for cervical cancer, and for all other conditions.

Position Statement

Summary

- Tivdak (tisotumab vedotin) is an intravenously administered tissue factor (TF)-directed antibody-drug conjugate (ADC) that delivers chemotherapy to TF expressing cancer cells.
- The intent of this policy is to allow coverage of Tivdak (tisotumab vedotin) in the clinical setting described above (in the coverage criteria), where it has been evaluated for efficacy, up to the dose shown to be safe in clinical trials. FDA approval of Tivdak (tisotumab vedotin) was based on low quality data from a single, small, non-comparative, non-blinded study that evaluated an endpoint that has not been proven to predict clinical benefit.
- Tivdak (tisotumab vedotin) was evaluated as a monotherapy in patients with recurrent of metastatic cervical cancer that progressed after one or two lines of prior therapy, at least one of which was doublet chemotherapy, the current front-line standard of care (SOC).
- In the pivotal clinical study, Tivdak (tisotumab vedotin) was found to temporarily slow or stop the growth of tumors in about one-quarter of the patients. Seven patients (7%) were considered to have a complete response. It is not known how temporarily impacting tumor growth ultimately affects clinical outcomes like overall survival or disease-associated symptom control.
- Tivdak (tisotumab vedotin) has only been used in the subsequent-line treatment setting. All patients enrolled in the clinical trial were of good performance status (PS) and were candidates for therapy with doublet chemotherapy regimens, the front-line SOC. Patients who were not fit for doublet chemotherapy (poor PS) were excluded from the trial. Therefore, the safety and efficacy of Tivdak (tisotumab vedotin) in patients with poor PS or those unable to tolerate doublet chemotherapy is unknown.

- It is not known how the efficacy of Tivdak (tisotumab vedotin) compares with other therapies used in the subsequent-line advanced cervical cancer treatment setting.
- Tivdak (tisotumab vedotin) carries a Boxed Warning for ocular toxicity, including severe vision loss and corneal ulceration. In some patients these ocular adverse events may persist or worsen even after treatment is withdrawn.
- Keytruda (pembrolizumab) is approved for use as an add-on to front-line chemotherapy doublet therapy for advanced cervical cancer when tumors express programmed death-ligand 1 [PD-L1; with a Combined Positive Score (CPS) ≥ 1] based on improved overall survival relative to the chemotherapy doublet alone. It is also approved as monotherapy in the subsequent-line setting for PD-L1-expressing tumors where the quality of evidence is similar to that of Tivdak (tisotumab vedotin). Keytruda (pembrolizumab) is more cost effective among these options. Therefore, Tivdak (tisotumab vedotin) is coverable only after use of Keytruda (pembrolizumab) for PD-L1 expressing cervical cancer.
- The National Comprehensive Cancer Network (NCCN) treatment guideline lists Tivdak (tisotumab vedotin) and Keytruda (pembrolizumab) among potential treatment options for advanced cervical cancer when there has been disease progression on or after front-line doublet chemotherapy.
- Tivdak (tisotumab vedotin) may be covered in doses up to 2 mg/kg (max of 200 mg) IV every three weeks until disease progression, the dose studied in the pivotal trial. The safety and effectiveness of higher doses have not been established.
- The safety and effectiveness of Tivdak (tisotumab vedotin) in conditions other than advanced cervical cancer have not been established.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Disease Background [1,2]

- When detected in early stages, cervical cancer is potentially curable. However, once it metastasizes to distant sites it is rarely curable, and treatment is palliative.
- Cisplatin is the most effective agent for metastatic cervical cancer. However, by the time the disease progresses to advanced stages, most patients are no longer sensitive to single-agent cisplatin due to its use as a radiosensitizing agent in earlier stages of the disease. For this reason, multi-agent cisplatin-containing regimens are used in metastatic disease.

Clinical Efficacy [1,3]

- The efficacy of Tivdak (tisotumab vedotin) was evaluated in a small, non-comparative, non-blinded study [innovaTV 204] that evaluated tumor response in patients with recurrent or metastatic cervical cancer that had progressed on or after prior doublet chemotherapy.
    * Nearly all enrolled patients (94%) had extra-pelvic metastatic disease.
    * All patients had good performance status (PS) and prior doublet chemotherapy (either cisplatin plus paclitaxel or topotecan plus paclitaxel) with or without bevacizumab. Patients in the study had at least one, but no more than two prior therapies in the advanced disease setting.
    * Patients with any histology were included in the study; however, those with squamous cell carcinoma made up the majority (68%) of the population.
    * Partial tumor response was observed in 24% of patients, with 7 patients (7%) achieving a complete response. The median duration of response was 8.3 months.
- There is currently no data comparing Tivdak (tisotumab vedotin) with any other therapy used in the management of advanced cervical cancer, and there is no data evaluating clinical outcomes such as survival or symptom control.
- A phase 3 randomized controlled trial (RCT) studying Keytruda (pembrolizumab) as an add-on therapy to front-line doublet chemotherapy in advanced cervical cancer demonstrated improved overall survival with this combination relative to doublet chemotherapy alone. Keytruda (pembrolizumab) has also been studied and is approved as monotherapy for PD-L1-expressing (CPS $\geq$ 1) advanced cervical cancer when used in the subsequent-line treatment setting where the quality of evidence is similar to that of Tivdak (tisotumab vedotin). [4,5]
- The National Comprehensive Cancer Network (NCCN) cervical cancer guideline lists Tivdak (tisotumab vedotin) as a treatment option for recurrent or metastatic cervical cancer after progression on standard of care chemotherapy. Pembrolizumab is listed as preferred option in this population when tumors express PD-L1 (CPS $\geq$ 1). [2]

Investigational Uses [6,7]

- There is no published information evaluating the safety and efficacy of Tivdak (tisotumab vedotin) in disease settings other than as subsequent-line therapy for advanced cervical cancer.
- The NCCN Compendium does not currently recommend Tivdak (tisotumab vedotin) for any uses other than second- or subsequent-line treatment of advanced cervical cancer.

Safety [1 ,5]

- Tivdak (tisotumab vedotin) carries a Boxed Warning for potentially serious ocular toxicity, including severe vision loss and corneal ulceration. Ocular adverse events (AEs) may persist or worsen even after treatment is withdrawn.
- Other serious AEs include peripheral neuropathy, hemorrhage, and pneumonitis.

Cross References
Keytruda, pembrolizumab, Medication Policy Manual, Policy No. dru367

References

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Revision History

Revision Date	Revision Summary
12/7/2023	No criteria changes with this annual review.
12/9/2022	• Updated standard language in policy. • No changes to coverage criteria with this annual update.
3/18/2022	New policy (effective 4/15/2022). Limits coverage to monotherapy in patients with recurrent or metastatic cervical cancer whose disease has progressed on or after doublet chemotherapy and, for tumors that express PD-L1 (CPS ≥ 1), pembrolizumab unless contraindicated or not tolerated.

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Medication Policy Manual | **Policy No:** dru696

Topic: Neonatal Fc Receptor (FcRn) Antagonists:

- Rystiggo, rozanolixizumab
- Vyvgart, efgartigimod alfa-fcab
- Vyvgart Hytrulo, efgartigimod alfa and hyaluronidase-qvfc

Date of Origin: April 15, 2022

Committee Approval Date: December 12, 2024 | **Next Review Date:** 2025

Effective Date: January 15, 2025

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Neonatal Fc receptor (FcRn) antagonists are medications used in specific types of generalized myasthenia gravis (gMG) and chronic inflammatory demyelinating polyneuropathy (CIDP). FcRn antagonists target the immune response in patients with gMG and CIDP [bind to the neonatal Fc receptor, resulting in the reduction of circulating immune globulin G (IgG)].

Policy/Criteria

Most contracts require pre-authorization approval of efgartigimod-containing products prior to coverage.

I. Continuation of therapy (COT): Neonatal Fc Receptor (FcRn) antagonists (as listed in Table 1) may be considered medically necessary for COT when criteria A, B, and C are met.

A. One of the following (1, 2, or 3):

1. For diagnoses NOT listed in the coverage criteria below, criteria a and b must be met:

a. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

b. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

2. For diagnoses listed in the coverage criteria below, criteria a and b must be met:

a. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

b. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

3. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

AND

B. Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, Site of Care Review, dru408].

AND

C. "Administration, Quantity Limitations, and Authorization Period" below applies, as well as "Investigational Uses" for combination therapy.

Please note: *Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Neonatal Fc receptor (FcRn) antagonists (as listed in Table 1) may be considered medically necessary when clinical documentation (including, but not limited to chart notes) confirming that criteria A and B below are met:

A. Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, Site of Care Review, dru408].

AND

B. One of the following diagnostic criteria 1 or 2 below is met:

1. A diagnosis **generalized myasthenia gravis** (gMG) when criteria a through d below are met:

a. The diagnosis has been established by or in consultation with a neurologist who is a sub-specialist in neuromuscular disorders.

AND

b. One of the following specific antibody criteria (i or ii) below is met:

i. A positive serologic test for anti-acetylcholine receptor (anti-AChR) antibodies.

OR

ii. ***For Rystiggo (rozanolixizumab) only***: A positive serologic test for anti-muscle specific tyrosine kinase (MuSK) antibodies.

AND

c. Prior to starting neonatal Fc receptor (FcRn) antagonists, documentation of a total myasthenia gravis activities of daily living (MG-ADL) score of ≥ 5 OR a non-ocular MG-ADL score of ≥ 3.

AND

d. Standard MG treatment is documented as ineffective (lack of MG symptom control as verified by a MG scoring tool), unless all options listed below are documented as medically contraindicated or not tolerated. Standard MG therapy is defined as both criteria i and ii below.

i. At least two non-steroidal immunomodulating therapies including non-steroidal immunosuppressive therapies given continuously over the last 12 months: azathioprine, cyclosporine, mycophenolate, tacrolimus, methotrexate, or cyclophosphamide; chronic intravenous immune globulin (IVIG) given at least monthly over at least the past six months; plasmapheresis/plasma exchange (PLEX) given at least four times in the past 12 months; or rituximab given for at least 3 months.

PLEASE NOTE: Worsening of MG symptoms during IST dose taper is not considered documentation of "ineffective." Use of short-term IVIG as needed for myasthenic crisis will not satisfy this criterion.

AND

ii. If anti-acetylcholine receptor (anti-AChR) antibody positive, the patient has had a thymectomy.

OR

2. ***For Vyvgart Hytrulo (efgartigimod alfa and hyaluronidase-qvfc) only:*** A diagnosis of **chronic inflammatory demyelinating polyneuropathy (CIDP)** when criteria a through d below are met:

a. The diagnosis has been established by or in consultation with a neurologist.

AND

b. All of the following diagnostic criteria are met (i through v):

i. Progressive or relapsing proximal (upper arms, shoulders, hips and upper legs) **and** distal (hands, feet, lower arms and lower legs) muscle weakness of at least two limbs.

AND

ii. The muscle weakness is defined as developing over at least 8 weeks.

AND

iii. Reduced or absent tendon reflexes (areflexia) in at least two limbs.

AND

iv. Documented significant functional disability.

AND

v. Documentation of slowed nerve conduction velocity on electromyogram (EMG)/nerve conduction study (NCS) involving at least two nerves (median, ulnar, peroneal or tibial).

AND

c. Documentation of baseline symptoms with a standardized CIDP disability or impairment scale score, including, but not limited to, the Inflammatory Neuropathy Cause and Treatment (INCAT) scale, the Inflammatory Rasch-built Overall Disability Scale (I-RODS), or grip strength score using handheld dynamometry.

AND

d. Standard CIDP treatment is documented as ineffective (lack of CIDP symptom control as verified by a CIDP scoring tool **and** a lack of improvement in relapse frequency), unless all options

listed below are documented as medically contraindicated or not tolerated. Standard CIDP treatment is defined as use of at least TWO options listed below (i, ii, iii):

i. Immune globulin replacement (IVIG/SCIG), given at least monthly over at least 6 months.

ii. Corticosteroids, daily or pulsed, given at least weekly over at least 6 months.

iii. Plasmapheresis (plasma exchange/PLEX), given at least four times over 12 months.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers neonatal Fc receptor (FcRn) antagonists (as listed in Table 1) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, neonatal Fc receptor (FcRn) antagonists (as listed in Table 1) will be covered in quantities as follows:

Table 1. Neonatal Fc receptor (FcRn) antagonists

Drug	Initial authorization	Reauthorization
Rystiggo (rozanolixizumab)	<100 kg: up to thirty-six 280 mg vials in a 6-month period	<100 kg: up to seventy-two 280 mg vials in a 12-month period
	≥100 kg: up to fifty-four 280mg vials in a 6-month period	≥100 kg: up to one-hundred eight 280mg vials in a 12-month period
Vyvgart (efgartigimod)	Up to sixteen doses in a 6-month period, up to 10 mg/kg/dose, not to exceed 1,200 mg/dose	Up to thirty-two doses in a 12-month period, up to 10 mg/kg/dose, not to exceed 1,200 mg/dose
Vyvgart Hytrulo (efgartigimod hyaluronidase)	**gMG:** Up to sixteen doses in a 6-month period, up to 1,008 mg per dose **CIDP:** Up to twenty-six doses in a 6-month period, up to 1,008mg per dose.	**gMG:** Up to thirty-two doses in a 12-month period, up to 1,008 mg per dose **CIDP:** Up to fifty-two doses in a 12-month period, up to 1,008mg per dose.

C. Authorization **shall** be reviewed initially at 6 months then at least every 12 months to confirm that current medical necessity criteria are met, and that the medication is effective. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that the medication is providing clinical benefit, including disease stability or improvement must be provided, relative to

baseline symptoms. A standard disease-specific scoring tool must be included.

Specifically:

1. For gMG: the total myasthenia gravis activities of daily living (MG-ADL) score, total quantitative myasthenia gravis (QMG) score, and/or myasthenia gravis composite (MGC) scale.

2. For CIDP: the Inflammatory Neuropathy Cause and Treatment (INCAT) score, the Inflammatory Rasch-built Overall Disability score (I-RODS) and/or a grip strength score using a hand-held grip dynamometer or vigorimeter.

IV. Neonatal Fc receptor (FcRn) antagonists (as listed in Table 1) are considered investigational when used for all other conditions, including but not limited to:

A. Vyvgart, Vyvgart Hytrulo (efgartigimod): Myasthenia gravis with MUSK antibodies or antibodies other than anti-AChR.

B. Use in combination with other targeted therapies for myasthenia gravis or CIDP (such as intravenous or subcutaneous immunoglobulin, other FcRn antagonists or complement inhibitors [Soliris (eculizumab), Ultomiris (ravulizumab)])

C. Dosing of efgartigimod-containing products for gMG sooner than 50 days from the start of the previous cycle.

D. Dosing of Rystiggo (rozanolixizumab) sooner than 63 days from the start of the previous cycle.

E. Vyvgart Hytrulo (efgartigimod hyaluronidase): Guillain-Barré syndrome (GBS), auto-immune nodopathies, monoclonal gammopathies (amyloidosis, multiple myeloma etc.), diabetic neuropathy, neuropathies other than CIDP etc.

Position Statement

Summary

- The intent of the policy is to allow for coverage of neonatal Fc receptor (FcRn) antagonists for generalized myasthenia gravis (gMG) and chronic inflammatory demyelinating polyneuropathy (CIDP) when managed by a specialist, limit to more severe disease, and encourage the use of lower cost therapies (when appropriate), and limit coverage to doses studied and shown to be safe and effective in clinical trials.
- Myasthenia gravis (MG) is a rare autoimmune disease arising from T cell-dependent immunologic attack of AChR, muscle-specific tyrosine kinase (MuSK), and/or other receptors found on the postsynaptic neuromuscular junction, resulting in striated muscle weakness.
- Approximately 10-15% of all MG cases are refractory despite corticosteroids or steroid-sparing immunosuppressive agents. Neonatal Fc receptor (FcRn) antagonists are coverable for the treatment of gMG when front-line therapies are not effective.
- Chronic inflammatory demyelinating polyneuropathy (CIDP) is an acquired, immune-mediated neuropathy that affects peripheral nerves, characterized by a progressive (more common) or relapsing-remitting course of proximal and distal muscle weakness.
    * The presentation of CIDP is usually over the course of several months or longer. The diagnosis is dependent on progression or relapse over a course of 8 weeks or more.[1]
    * The diagnosis of CIDP is based on a combination of clinical symptoms (proximal and distal muscle weakness of upper and lower limbs, sensory involvement in at least two limbs, and absent or reduced tendon reflexes in all limbs), nerve conduction study findings, and other supportive criteria (laboratory findings, imagine, nerve biopsy, cerebral spinal fluid examination etc.).[1]
    * Nerve conduction studies are the most important diagnostic tool to support the clinical diagnosis of CIDP; nerve conduction study diagnostic criteria involve assessments for demyelination in at least 2 nerves (median, ulnar, peroneal, or tibial). [1]
    * There is a lack of *consistent* diagnostic criteria used in clinical practice for the diagnosis of CIDP. Therefore, coverage of Vyvgart Hytrulo (efgartigimod hyaluronidase) for CIDP is limited to CIDP, as defined by the diagnostic inclusion criteria from the pivotal trial. Use of Vyvgart Hytrulo (efgartigimod hyaluronidase) in patients with CIDP defined from other diagnostic criteria has not been studied and the use of Vyvgart Hytrulo (efgartigimod hyaluronidase) in these patients is considered investigational.
    * There are other treatment alternatives for CIDP, such as corticosteroids or immunoglobulin replacement therapy, with years of clinical experience, endorsed by guidelines and significantly less costly as compared to Vyvgart Hytrulo (efgartigimod hyaluronidase).
- Neonatal Fc receptor (FcRn) antagonists provide new treatment options for refractory gMG and CIDP. While the clinical data is promising, there are several limitations in the body of evidence. Use should be limited to patients who have failed other standard

treatment options, as detailed in the coverage criteria. Standard therapies recommended by treatment guidelines for management of MG include acetylcholinesterase (ACh) inhibitors (pyridostigmine), corticosteroids, various non-steroidal immunosuppressant therapy (NIST), intravenous immunoglobulin (IVIG), plasmapheresis/plasma exchange (PLEX), and thymectomy, unless contraindicated. [2-6]

- Standard therapies recommended by treatment guidelines for management of CIDP include corticosteroids, intravenous or subcutaneous immunoglobulin, and plasmapheresis/plasma exchange (PLEX). [1]
- Disease specific scoring tools are used for baseline assessment and monitoring of disease progression, as well as response to therapy(s).
    * MG-ADL is a scoring tool used in clinical practice, along with MG composite score, for monitoring progression of MG and response to therapies.[7]
    * Despite not being used regularly in clinical practice, the INCAT score, is a commonly used, reliable and validated measure used in clinical trials for CIDP.
    * The INCAT, I-RODS and grip strength scores are in guidelines as recommended *objective* measures for monitoring response to treatment, when compared to their baseline values.[1]
- Efgartigimod-containing products have not been studied and shown to be safe or effective in patients other than specified in the coverage criteria, including:
    * Patients with MG and other antibodies, including MuSK antibodies, antibodies to the agrin receptor low-density lipoprotein receptor–related protein 4 (LRP4), or any other antibodies. Efgartigimod has been studied in both AChR antibody positive and MuSK antibody positive populations.
    * Patients with less severe MG (without generalized MG symptoms) or those in myasthenic crisis (MGFA Class V).
    * Patients with any other type of neuropathy, or conditions including, but not limited to, Guillain-Barré syndrome (GBS), auto-immune nodopathies, monoclonal gammopathies (amyloidosis, multiple myeloma etc.), diabetic neuropathy etc.
- The safety and efficacy of neonatal Fc receptor (FcRn) antagonists in combination with other targeted MG therapies, such as Soliris (eculizumab) or Ultomiris (ravulizumab), have not been established. In addition, there is insufficient evidence to support the use of chronic maintenance IVIG in combination with FcRn antagonists and/or compliment inhibitors for either MG or CIDP.
- Neonatal Fc receptor (FcRn) antagonists may be covered for refractory MG at the doses proven to be safe and effective in clinical trials, as detailed in the coverage criteria. Efgartigimod-containing products when used to treat gMG have not been studied when given more frequently than every 50 days per cycle. Rystiggo (rozanolixizumab) when used to treat gMG has not been studied when given more frequently than every 63 days per cycle.

Disease Background

Generalized Myasthenia Gravis (gMG) [2-6]

- Myasthenia gravis (MG) is a rare autoimmune disease arising from T cell-dependent immunologic attack of AChR, muscle-specific tyrosine kinase (MuSK), and/or other receptors found on the postsynaptic neuromuscular junction, resulting in striated muscle weakness.
    * MG presents with painless, fluctuating, fatigable weakness of specific muscle groups. Initially, patients most frequently present with ocular MG of the eyelids and extraocular muscles, presenting with asymmetric ptosis and diplopia. As weakness extends beyond ocular muscles, the disease progresses into gMG.
    * Approximately 10-15% of all MG cases consist of refractory gMG that presents with severe debilitating muscle weakness despite substantial use of long-term corticosteroids or multiple steroid-sparing immunosuppressive agents, resulting in substantial negative effects on activities of daily living and quality of life. Neonatal Fc receptor (FcRn) antagonists are coverable for the treatment of gMG when front-line therapies are not effective.
- Standard therapies recommended by treatment guidelines for management of MG include acetylcholinesterase (ACh) inhibitors (pyridostigmine), corticosteroids, various non-steroidal immunosuppressant therapy (NIST), intravenous immunoglobulin (IVIG), plasmapheresis/plasma exchange (PLEX), and thymectomy.
    * Acetylcholinesterase inhibitors are used for temporary symptomatic relief of MG symptoms, by slowing the breakdown of acetylcholine at the neuromuscular junction. However, their use is limited as an adjunct therapy to immunotherapy in those with residual or refractory MG or for treatment of ocular and mild gMG in those who cannot receive immune suppression.
    * Corticosteroids are the most widely used immune modulator for MG. Corticosteroids are effective in ocular MG and in patients with gMG with unsatisfactory responses to acetylcholinesterase inhibitors; however, they are associated with significant dose-dependent adverse events and should not be used for extended durations.
    * Azathioprine, cyclosporine, and mycophenolate mofetil are standard non-steroidal immunosuppressant therapy (NIST) and act as steroid-sparing agents. Other options include cyclophosphamide, methotrexate, and tacrolimus.
        ▪ Onset of effect is slow (up to 9-12 months). Once goals are met, steroids may be slowly tapered; however, many patients require long-term low-dose steroids for symptom control.
        ▪ Guidelines recommend dose adjustments no more frequently than every 3 to 6 months.
        ▪ Once treatment effective is achieved and doses are maintained for six months to two years of therapy, NIST doses should be tapered to the lowest effect dose
    * Plasma exchange/plasmapheresis (PLEX) and IVIG provide short-term symptomatic relief during exacerbations for surgical preparation or in patients

with septicemia through downregulating autoantibodies and/or inducing anti-idiopathic antibodies. IVIG may be a maintenance treatment option for patients intolerant to or not responding to an adequate course of non-steroidal immunosuppressive therapy (NIST).[2]

* Patients with thymoma should undergo thymectomy. In non-thymomatous patients, thymectomy is a treatment option to minimize need for immunotherapy (either avoid, dose minimize, or use for refractory MG symptoms). However, thymectomy may not be indicated in the following types of patients:
    - Unstable MG patients (medically not possible).
    - Patients with antibodies other than AChR, including MuSK, low-density lipoprotein receptor–related protein 4 (LRP4). (thymectomy is not indicated, based on lack of efficacy in the currently available evidence).[3 8]
    - Of note, other targeted therapy for AChR antibody positive MG includes complement inhibitors, such as Soliris (eculizumab) or Ultomiris (ravulizumab).

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) [1 9 10]

- Chronic inflammatory demyelinating polyneuropathy (CIDP) is an acquired, immune-mediated neuropathy that affects peripheral nerves.
    * CIDP is characterized by a progressive (more common) or relapsing-remitting course of proximal and distal muscle weakness.
    * The presentation of CIDP is usually over the course of several months or longer. The diagnosis is dependent on progression or relapse over a course of 8 weeks or more.
    * It typically follows a progressive course; however, it can also be remitting and relapsing.
- Common clinical features include proximal muscle weakness (climbing/descending stairs, rising from a seated position, difficulty walking and frequent falls), distal muscle weakness (scuffing or tripping over the feet), difficulty with fine motor tasks, diminished or absent reflexes (areflexia) and tremor.
- The exact cause of CIDP and its variants is unknown; current evidence supports involvement of both cellular (activation of T cells, cytokines, tumor necrosis factor, interferons, and interleukins) and humoral (immunoglobulin G) components of the adaptive immune system.
- The diagnosis of CIDP is based on electrodiagnostic criteria (conduction abnormalities), pathologic features of nerve demyelination and responsiveness to immunomodulatory treatments. The diagnosis of probable or definite CIDP in the pivotal trial was based on criteria from the 2010 European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) guidelines, which recommend a combination of clinical, electrodiagnostic and laboratory features with exclusions to eliminate other disorders that may appear as CIDP.

CIDP Guidelines[1]

- Early administration of treatment in CIDP is important to minimize long-term disability and to improve symptoms and function. Most patients are significantly impaired and require treatment, often with multiple medication trials to optimize response and reduce relapse occurrence.
- The first-line treatments for CIDP include corticosteroids, plasmapheresis (plasma exchange), and immunoglobulin G administration [intravenous (IVIG) or subcutaneous (SCIG)].
- The 2021 guidelines from the European Academy of Neurology and Peripheral Nerve Society (EAN/PNS) consider the above treatments as first line for the treatment of CIDP:
    * IVIG or corticosteroids are strongly recommended as initial (induction) treatment.
    * Plasma exchange is strongly recommended if IVIG and corticosteroids are ineffective.
    * For maintenance treatment, IVIG, SCIG, or corticosteroids are recommended.
- Per this guideline, there is insufficient evidence to demonstrate greater efficacy of one product over another for the treatment of CIDP.
- Guidelines have not been updated since the FDA approval of efgartigimod alfa and hyaluronidase-qvfc for CIDP.

Clinical Efficacy

Generalized Myasthenia Gravis (gMG)[7 11 12]

- The evidence for efgartigimod-containing products in gMG is limited. Efgartigimod was approved for the treatment of gMG based on one 26-week, phase 3, ADAPT study, comparing efgartigimod to placebo in patients who had a gMG with a MG-ADL score $\geq$ 5 and who were on stable doses of $\geq$ 1 treatment for gMG. The trial included both AChR antibody positive and negative patients but only a small portion (23%) of patients were AChR antibody negative. The response rate in AChR antibody negative patients was similar to that of placebo but the evidence is limited due to the small sample size.
    * In ADAPT, the primary endpoint of proportion of AChR-ab+ patients who were MG-ADL responders (≥2-point MG-ADL improvement sustained for ≥4 weeks) in the first treatment cycle (8 weeks) was higher in the efgartigimod arm versus the placebo arm.
    * Most patients (~70%) in the ADAPT study had at least one prior non-steroidal immunosuppressant agent; ~70% had prior thymectomy.
    * Although patients were permitted a 7-week cycle duration between cycles (time from first infusion of one cycle to the first infusion of the next cycle), the median duration between cycles was 10 weeks.
    * The ADAPT study was a 26-week study period thus it may be insufficient to comprehensively assess the efficacy of a drug therapy in a chronic disease, including the durability of treatment effect.

- The evidence for rozanolixizumab is limited to one double-blind, placebo-controlled, phase 3 study (MycarinG) , in which patients who are either AChR+ or MuSK+ with refractory moderate to severe gMG were randomly assigned to receive subcutaneous infusions of 7 mg/kg rozanolixizumab, 10 mg/kg rozanolixizumab, or placebo once a week for 6 weeks followed by 8 weeks of observation.[13]
    * Patients were required to have a Myasthenia Gravis Activities of Daily Living (MG-ADL) score of at least 3 (with at least 3 points from non-ocular symptoms) at baseline. The median baseline total MG-ADL score was 8.
    * The primary efficacy endpoint was the comparison of the change from baseline between treatment groups in the MG-ADL total score at day 43. A statistically clinically significant difference favoring rozanolixizumab was observed in the MG-ADL total score change from baseline [-3.4 points in rozanolixizumab-treated groups vs -0.8 points in the placebo-treated group ($p<0.001$)].
    * More patients in the rozanolixizumab arms had a clinically significant increase in MG-ADL score versus placebo.
    * Due to the short study duration, the long-term safety and efficacy of rozanolixizumab is unknown at this time.
- None of the trials of FcRn antagonists allowed the use of these therapies in combination with either IVIG and/or complement inhibitors.

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) [9 14]

- The FDA-approval of efgartigimod hyaluronidase for the treatment of CIDP was based on one unpublished placebo-controlled trial (ADHERE, N=322). The trial included an open-label period (stage A) to identify patients who had evidence of improvement (responders) with the use of efgartigimod hyaluronidase, who then entered a randomized-double-blind, placebo-controlled withdrawal period (stage B).
    * All enrolled subjects:
        - Had a diagnosis of progressing or relapsing, probable or definite CIDP, according to criteria from the 2010 criteria from the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS).
        - Had a baseline INCAT score ≥ 2 from the leg disability score or ≥ 3 without specifics to leg or arm scores.
        - Were currently receiving either standard of care therapy (intravenous or subcutaneous immunoglobulin replacement or corticosteroids) or no previous treatment. All current treatments were discontinued prior to the open label stage A.
    * Concomitant treatment with any other biologic agent, FcRn antagonist, or immunoglobulin (IVIG/SCIG) was not allowed.
    * All enrolled subjects received weekly efgartigimod hyaluronidase SC for 12 weeks (Stage A; n=322). Responders from stage A were randomized to efgartigimod hyaluronidase SC or placebo for 48 weeks (stage B efficacy phase; n=221). Non-responders (31% of enrolled patients from Stage A) did not continue to Stage B.

* The primary efficacy endpoint was the time to clinical deterioration (relapse), defined as a 1-point increase in the adjusted Inflammatory Neuropathy Cause and Treatment (aINCAT) score.
* The FDA approval of efgartigimod hyaluronidase SC for CIDP was based on unpublished trial evidence, that has not been peer-reviewed. At this time, there are significant unknowns to the trial to define who is most likely to respond, including the percent of patients who were previously treated with standard of care (corticosteroids and/or immunoglobulins) and in whom standard of care was ineffective or not tolerated.
    - Based on the abstract presentation, a 61% reduction in the relapse risk was demonstrated in subjects who received active treatment (HR=0.39; p=0.000039), compared to placebo. Subjects who received efgartigimod hyaluronidase experienced a longer time to clinical deterioration (relapse) compared to those who received placebo.
    - However, at this time, the primary endpoint results [time to clinical deterioration (relapse)] are not available, and the true clinical efficacy of efgartigimod hyaluronidase cannot be evaluated.
    - Despite the reported relapse risk reduction of 61%, it is important to remember that any outcome analysis is based only on responders from the open-label phase. Use of an open-label trial design favors the active treatment arm. Therefore, the expected clinical response rate in all-comers, as well as patients in clinical practice, is unknown.
* The aINCAT score is a validated, commonly used and reliable measure of symptomatic disability of patients with CIDP, that takes into account upper and lower limb function. A decrease in the score of ≥ 1 point is considered clinically significant for symptom improvement (minimal clinically important difference, MCID).

Investigational Uses[12 15]

- Neonatal Fc receptor (FcRn) antagonists are being studied for a variety of other indications. However, at this time, there is insufficient evidence to establish the safety and efficacy of neonatal Fc receptor (FcRn) antagonist sin any other indications (other than detailed in the coverage criteria).
- There are no published clinical trials evaluating the safety or efficacy of neonatal Fc receptor (FcRn) antagonists given in combination with one another, with a complement inhibitor such as Soliris (eculizumab) or Ultomiris (ravulizumab), or in combination with IVIG or SCIG.
- Evidence for the use of efgartigimod-containing products in MUSK-antibody positive or AChR-Ab negative population is limited. Although the ADAPT study included AChR-Ab negative patients, the number of patients was low (n=38), and results of this subgroup analysis were underpowered (68% response rate in the efgartigimod arm versus 63% in the placebo arm). Only six patients in the ADAPT trial were MUSK-antibody positive.

- The safety of initiating subsequent cycles of efgartigimod-containing products sooner than 50 days or Rystiggo (rozanolixizumab) sooner than 63 days from the start of the previous treatment cycle has not been established.

Safety [11 12 15]

- Although neonatal Fc receptor (FcRn) antagonists do not have a boxed warning for life-threatening and fatal meningococcal infections, long-term safety data is lacking and there are concerns for infections associated with prolonged lowering of IgG. In the ADAPT and MycarinG trials, 23-46% of patients had an adverse event related to infections, most of which were mild to moderate severity.
- A post-observation period is required to monitor for hypersensitivity reactions.

Dosing [11 12 15]

- In the ADAPT trial, patients on efgartigimod were given 10 mg/kg IV (1200 mg for those weighing 120 kg or more) once weekly x 4 weeks. The interval was variable but no sooner than 50 days after initiation of the previous cycle. Patients were re-dosed only when they no longer had a clinically meaningful improvement on the MG-ADL.
- In an extension study of rozanolixizumab, the minimum time for initiating subsequent treatment cycles, was 63 days from the start of the previous treatment cycle. On average, patients initiated 4 cycles of rozanolixizumab in one year (range 1 to 7 cycles).
- In the ADHERE trial, the dose of efgartigimod hyaluronidase for CIDP was limited to once weekly, subcutaneous injections of 1,008 mg of efgartigimod and 11,200 units of hyaluronidase.

Cross References
Complement Inhibitors, Medication Policy Manual, Policy No. dru385
Site of Care Review, Medication Policy Manual, Policy No. dru408
Immune Globulin Replacement Therapy, Medication Policy Manual, Policy No. dru020

Codes	**Number**	**Description**
HCPCS	J9332	Injection, efgartigimod alfa-fcab (Vyvgart), 2mg
HCPCS	J9334	Injection, efgartigimod alfa 2mg and hyaluronidase-qvfc 11,200 units, (Vyvgart Hytrulo)
HCPCS	J9333	Injection, rozanolixizumab-noli (Rystiggo), 1 mg

Appendix 1: Medications that may unmask or worsen myasthenia gravis *
Aminoglycosides
Amantadine
Antiarrhythmics (procainamide, propafenone, quinidine)
Antiepileptics (various, carbamazepine, gabapentin, phenytoin, etc.)
Cancer immunotherapies, including but not limited to: Anti-programmed death receptor-1 monoclonal antibodies (PD1s, PDL-1s; Opdivo [nivolumab], Keytruda [pembrolizumab], etc.) Yervoy (ipilimumab) Provenge (sipuleucel-T)
Antihistamines (diphenhydramine)
Beta-blockers
Calcium channel blockers (felodipine, verapamil)
Colchicine
Erythromycins (azithromycin, clarithromycin, clindamycin)
Plaquenil (hydroxychloroquine)
Interferons (various)
Lithium
Magnesium
Neuromuscular blockers (succinylcholine, etc.)
Opioids
Phenothiazines (haloperidol)
Proton pump inhibitors (lansoprazole, omeprazole)
Quinine
Quinolones (ciprofloxacin, levofloxacin, etc.)
Statins (pravastatin, etc.)

*Including, but not limited to this list. Medication lists will be reviewed in full versus compendium (such as DrugDex).

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Revision History

Revision Date	Revision Summary
12/12/2024	Effective 1/15/25: • No change to policy intent. Clarified authorization durations (initial authorization is for 6 months, followed by 12 months for reauthorizations). • Corrected v.3 criteria II.B.1.c. clerical error of missing MG-ADL parameter (reason for expedited effective date).
9/19/2024	Added coverage criteria for Vyvgart Hytrulo (efgartigimod hyaluronidase) for the treatment of chronic inflammatory demyelinating polyneuropathy (CIDP).
12/7/2023	• Renamed policy to "FcRn Antagonists." • Added Rystiggo (rozanolixizumab) to policy. • Criteria modified to include coverage for MuSK+ (for rozanolixizumab [Rystiggo]) • Added non-ocular MG-ADL score > or = 3 or total score of > or = 5. • Criteria simplified to require two prior non-steroidal immunomodulating therapies. • Use with other targeted therapies or IVIG is investigational. • Initial authorization duration extended to 6 months, reauthorization 12 months.
9/14/2023	• Renamed policy to "Efgartigimod-containing medications". • Added of Vyvgart Hytrulo (efgartigimod hyaluronidase-qvfc) to policy.
3/18/2022	New policy (effective 4/15/2022). Limits use of Vyvgart (efgartigimod) for generalized myasthenia gravis (gMG) when managed by a specialist, limit to more severe disease and encourage the use of lower cost therapies (when appropriate), and limit coverage to doses studied and shown to be safe and effective in clinical trials.

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Medication Policy Manual

Policy No: dru697

Topic: PCSK9 Inhibitors

- Leqvio, inclisiran
- Praluent, alirocumab
- Repatha, evolocumab

Date of Origin: June 1, 2022

Committee Approval Date: March 16, 2023

Next Review Date: 2024

Effective Date: June 1, 2023

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medical Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are used in the treatment of atherosclerotic cardiovascular disease (ASCVD) and familial hypercholesteremia.

Policy/Criteria

Most contracts require pre-authorization approval of PCSK9 inhibitors prior to coverage.

I. Continuation of therapy (COT): PCSK9 inhibitors may be considered medically necessary for COT when criteria A, B, or C **AND** D below is met.

A. For diagnoses NOT listed in the coverage criteria below, full policy criteria must be met for coverage.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

AND

D. **For Leqvio (inclisiran) only:** Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, Site of Care Review, dru408].

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): PCSK9 inhibitors may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A and B below are met.

A. **Leqvio (inclisiran) only:** Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, Site of Care Review, dru408].

AND

B. At least one of the following diagnostic criterion 1, 2 or 3 below is met.

1. **Leqvio (inclisiran), Praluent (alirocumab), Repatha (evolocumab): Heterozygous familial hypercholesterolemia** (HeFH) when both criteria a and b are met.

a. The requested PCSK9 inhibitor has been prescribed by or in conjunction with a specialist in cardiology or lipid management and there is clinical documentation of at least one of the following (i, ii, or iii):

i. A definitive diagnosis of FH using Simon Broome diagnostic criteria or Dutch Lipid Clinic Network criteria (see *Appendices 1 and 2*).

OR

ii. An untreated low-density lipoprotein cholesterol (LDL-C) of ≥ 190 mg/dL (or ≥ 160 mg/dL in patients less than 20 years of age) with at least one of the following:

1. Physical signs of FH, such as presence of tendon xanthomas, premature corneal arcus, tuberous xanthomas, or xanthelasma.

OR

2. Family History of FH.

OR

iii. Presence of a causal mutation for FH by DNA testing (e.g., a mutation in the *LDLR, APOB, PCSK9,* or *LDLRAP1* genes).

AND

b. Treatment with maximally tolerated lipid lowering therapy has failed to achieve an LDL-C of less than or equal to 100 mg/dL after at least 12 weeks of therapy. The treatment regimen must include all the following (i, ii, and iii), unless contraindicated or not tolerated:

i. A high-intensity statin (atorvastatin or rosuvastatin). If one high-intensity statin has not been tolerated due to statin-associated side effects, then at least one other statin must have been tried at a lower dose.

AND

ii. Ezetimibe.

AND

iii. **For Leqvio (inclisiran) only:** Praluent (alirocumab) or Repatha (evolocumab).

OR

2. **Praluent (alirocumab) or Repatha (evolocumab) only: homozygous familial hypercholesterolemia** (HoFH) when criteria a and b below are met:

a. The requested PCSK9 inhibitor has been prescribed by or in conjunction with a specialist in cardiology or lipid management and there is clinical documentation of at least one of the following (i or ii):

i. Genetic confirmation of two mutant alleles at the *LDLR, APOB, PCSK9,* or *LDLRAP1* gene locus.

OR

ii. An untreated low-density lipoprotein cholesterol (LDL-C) of > 500 mg/dL (or a treated LDL-C of > 300 mg/dL) with either (1 or 2):

1. Cutaneous or tendon xanthoma before age 10 years.

OR

2. Evidence of heterozygous familial hypercholesterolemia in both parents.

AND

b. Treatment with maximally tolerated statin therapy has been ineffective, contraindicated, or not tolerated.

OR

3. Leqvio (inclisiran), Praluent (alirocumab), Repatha (evolocumab): clinical atherosclerotic cardiovascular disease (ASCVD) when criteria a, b, and c below are met (see *Appendix 6* for definitions of ASCVD).

a. The requested PCSK9 inhibitor has been prescribed by or in conjunction with a specialist in cardiology or lipid management.

AND

b. The member is at very high risk for ASCVD events (see *Appendix 8*).

AND

c. Treatment with maximally tolerated lipid lowering therapy has failed to achieve an LDL-C of less than or equal to 70 mg/dL after at least 12 weeks of therapy. The treatment regimen must include <u>all the following</u> (i, ii, and iii), unless contraindicated or not tolerated.

i. A high-intensity statin (atorvastatin or rosuvastatin). If one high-intensity statin has not been tolerated due to statin-associated side effects, then at least one other statin must have been tried at a lower dose.

AND

ii. Ezetimibe.

AND

iii. **For Leqvio (inclisiran) only:** Praluent (alirocumab) or Repatha (evolocumab).

III. Administration, Quantity Limitations, Authorization Period

A. Regence Pharmacy Services considers Praluent (alirocumab) and Repatha (evolocumab) to be coverable only under the pharmacy benefit (as self-administered medications).

B. Regence Pharmacy Services considers Leqvio (inclisiran) to be coverable only

under the medical benefit (as a provider-administered medication).

C. When pre-authorization is approved, PCSK9 inhibitors will be authorized in the following quantities:

Medication	Authorization Limit
Praluent (alirocumab)	Up to 150 mg every 2 weeks or 300 mg every 4 weeks.
Repatha (evolocumab)	Up to 140 mg every other week or 420 mg once monthly.
Leqvio (inclisiran)	Loading Dose: Up to 284 mg initially followed by 284 mg in 3 months. Maintenance Dose: Up to 284 mg every 6 months.

D. Authorization may be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

IV. PCSK9 inhibitors are considered not medically necessary when used for:

A. Non-familial hyperlipidemia/hypercholesterolemia.

B. Primary prevention of atherosclerotic cardiovascular disease (ASCVD).

C. Primary prevention of ASCVD in patients who are statin-intolerant.

V. PCSK9 inhibitors are considered investigational when used for all other conditions, including but not limited to:

A. In combination with other PCSK9 inhibitors or Juxtapid (lomitapide).

Position Statement

Summary

- Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are subcutaneous medications indicated:
  * to reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established cardiovascular disease.
  * as an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia, HeFH) to reduce low-density lipoprotein cholesterol (LDL-C).
  * as an adjunct to diet and other LDL-lowering therapies (e.g., statins, ezetimibe, LDL apheresis) in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.
- American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines define clinical ASCVD as acute coronary syndromes, a history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease presumed to be of atherosclerotic origin.
- The intent of this policy is to limit coverage of PCSK9 inhibitors to patients with a confirmed diagnosis of HoFH, HeFH, or clinical ASCVD, who have tried and failed lower cost therapies (as detailed in the coverage criteria).
- 2018 AHA/ACC Guidelines on the Management of blood cholesterol recommend high-intensity statins for high-risk patients, such as those with clinical ASCVD or with HeFH. On average, high-intensity statins lower LDL-C by approximately ≥50%. Statins have been proven to reduce cardiovascular (CV) events and mortality; thus, they are the preferred treatment to reduce the risk ASCVD and recommended as the first-line treatment by multiple guidelines.
- AHA/ACC Guidelines recommend ezetimibe before PCSK9 inhibitors in patients with ASCVD. Although there is limited evidence supporting the strategy of ezetimibe before PCSK9 inhibitors, guidelines state that ezetimibe is widely available as a generic and has proven safety and tolerability along with CV outcomes data. [1]
- Based on results from the IMPROVE-IT study, ezetimibe has also been shown to modestly improve cardiovascular outcomes. Although, it was studied in a very narrow, high-risk population it is a treatment option in patients with clinical ASCVD or HeFH.
- The addition of ezetimibe to statin therapy typically reduces LDL-C by 15% to 30% in patients with hyperlipidemia.
- AHA/ACC Guidelines state that PCSK9 inhibitors are reasonable in patients with very high risk ASCVD who cannot achieve an LDL or < 70 mg/dL while on a high-intensity statin and ezetimibe.
- PCSK9 inhibitors have been studied in multiple placebo- or active-controlled phase 3 studies which included a variety of patients including those with HeFH and/or clinical ASCVD.

- Treatment with either Praluent (alirocumab) or Repatha (evolocumab) in combination with a statin improved CV outcomes. However, the magnitude of benefit was modest.
- CV outcomes data for Leqvio (inclisiran) is not yet available. The use of medications with proven CV benefits is required prior to coverage of Leqvio (inclisiran), as outlined in the coverage criteria, as the CV benefits of Leqvio (inclisiran) are unknown at this time.
- HeFH and HoFH may be diagnosed via clinical criteria, such as baseline LDL values, family history, and physical manifestations of FH, or through genetic testing. Commonly used diagnostic criteria include Simon Broome Diagnostic Criteria and Dutch Lipid Clinic Network Criteria for Heterozygous FH Diagnosis.
- Statins are also recommended as initial therapy for the treatment of HeFH. Non-statins may be considered in patients who are unable to reach target LDL-levels or who are statin intolerant. Although ACA/AHA guidelines do provide treatment recommendations for patients with HeFH, guidelines specifically for HeFH have been produced by the National Lipid Association (NLA) and European Atherosclerosis Society (EAS).
- NLA treatment guidelines for HeFH recommend targeting a 50% reduction in LDL-C from baseline; however higher risk patients may require a more aggressive treatment goal of less than 100 mg/dL. Patients will generally require treatment with multiple agents to achieve LDL-C goals.
- Statin-intolerance is not well defined. In a clinical trial of Praluent (alirocumab) in statin intolerant patients (defined as the inability to tolerate due to muscle symptoms at least two statins with at least one at the lower FDA-approved starting dose), over 70% of patients who were randomized to receive blinded atorvastatin 20 mg were able to complete the study. Although, this trial was conducted in a "statin intolerant" population, most of these patients were able to tolerate statin therapy, thus requiring trials of multiple statins prior to coverage of a PCSK9 inhibitor is warranted.
- 2018 AHA/ACC Guidelines state that in patients with statin-associated side effects that are not severe, it is recommended to reassess and to re-challenge to achieve a maximal LDL-C lowering by modified dosing regimen, an alternate statin or in combination with non-statin therapy.
- PCSK9 inhibitors have not been studied in combination with any other PCSK9 inhibitor or Juxtapid (lomitapide).
- PCSK9 inhibitors appear to be well-tolerated. However, additional long-term studies and clinical experience is needed with Leqvio (inclisiran).
- In late 2018, the manufacturer of Repatha (evolocumab) introduced new NDC's (beginning with 72511) at a significant discount. The previous (legacy) NDC's (beginning with 55513) have been discontinued as of December 31, 2019.

Clinical Efficacy

Praluent (alirocumab)

- The ODYSSEY OUTCOMES study evaluated the impact of Praluent (alirocumab) on cardiovascular outcomes in patients with a history of acute coronary syndrome (ACS) in the past 1 to 12 months. The primary endpoint was the composite of cardiovascular death, MI, stroke, and hospitalization for unstable angina. Patients were randomized to

either Praluent (alirocumab) 75 mg every two weeks or placebo. All patients were on background high-intensity statins or their maximally-tolerated dose of atorvastatin or rosuvastatin.

  * After a median follow-up of 2.8 years, Praluent (alirocumab) reduced the risk of the primary endpoint compared to placebo (9.5% vs. 11.1%, respectively; hazard ratio, 0.85; 95% CI, 0.78 to 0.93; P<0.001). The secondary endpoint of the composite of death from any cause, non-fatal MI, and non-fatal stroke also favored alirocumab compared to placebo (10.3% vs. 11.9%, respectively; hazard ratio 0.86; 95% CI 0.79 to 0.93; P<0.001).

- The body of evidence supports that Praluent (alirocumab) produces substantial reductions in LDL-C. [2 3]
  * The primary endpoint in the majority of Praluent (alirocumab) phase 3 studies was percent change in LDL-C.
  * Among ten placebo- and active controlled phase 3 studies, Praluent (alirocumab) reduced LDL-C by approximately 43 to 61 percent from baseline. The studies included a several populations, including those with HeFH and/or clinical ASCVD. Studies ranged in duration from 12 to 78 weeks. Results were statistically significant versus placebo and versus ezetimibe.
  * In patients with HoFH the mean LDL-C reduction was approximately 36%.[4]

Repatha (evolocumab)

- The FOURIER study evaluated the impact of evolocumab on cardiovascular outcomes in patients with clinical ASCVD. The primary endpoint was the composite of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization. Patients were randomized to either Repatha (evolocumab) or placebo and all patients were on background high or moderate intensity statin therapy. [5]
  * After a median follow-up of 26 months, evolocumab modestly reduced the risk of the primary endpoint compared to placebo (9.8% vs. 11.3%, respectively; hazard ratio, 0.85; 95% CI, 0.79 to 0.92; P<0.001).
  * Evolocumab also significantly reduced the risk of the key secondary composite of CV death, MI, or stroke compared to placebo (5.9% vs. 7.4%, respectively; hazard ratio, 0.80; 95% CI, 0.73 to 0.88; P<0.001). However, results for cardiovascular mortality alone were not statistically significant.
- The body of evidence supports that Repatha (evolocumab) produces substantial reductions in LDL-C. [6]
  * The primary endpoint in the majority of Repatha (evolocumab) phase 3 studies was percent change in LDL-C. Reductions in LDL-C ranged from 54% to 71% in patients with clinical ASCVD or HeFH. [6]
  * In patients with HoFH the mean LDL-C reduction was approximately 31%. [7]

Leqvio (inclisiran)

- The body of evidence supports that Leqvio (inclisiran) produces substantial reductions in LDL-C. [8 9]

    * The primary endpoint in the majority of Leqvio (inclisiran) phase 3 studies was percent change in LDL-C.
    * Reductions in LDL-C ranged from 40% to 51% in patients with clinical ASCVD or HEFH.
- Although the data continues to evolve, CV outcomes data for Leqvio (inclisiran) is not yet available. Of note, Praluent (alirocumab) or Repatha (evolocumab) in combination with a statin resulted in a modest improvement in CV outcomes in trials.
- Several outcomes trials have demonstrated that statins reduce the risks of cardiovascular and cerebrovascular events. [1]
    * Reduction in cardiovascular and cerebrovascular risk is not unique to any specific statin and has been demonstrated with many of the available statins in a variety of patient populations, such as in patients with coronary heart disease, high cholesterol levels, normal cholesterol levels, hypertension, diabetes, and previous stroke.
    * Several primary and secondary prevention trials with simvastatin, pravastatin, lovastatin, and atorvastatin consistently demonstrate that reductions in cardiovascular events correlate with LDL-C reduction.[10-12]

Guidelines

ASCVD

- The 2018 American College of Cardiology and American Heart Association (ACC/AHA) treatment guidelines state that PCSK9 inhibitors are reasonable for patients with very high risk ASCVD who cannot achieve an LDL or < 70 mg/dL while on a high-intensity statin and ezetimibe.
    * Very high risk is defined as a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk condition (see *Appendix 8*).
- For patients with ASCVD the first goal is to achieve a 50% or more reduction in LDL-C, but if LDL-C levels remain 70 mg/dL or great additional treatment with ezetimibe is considered reasonable.
- Guidelines acknowledge that the evidence supporting the use of ezetimibe before PCSK9 inhibitors is limited. Although, patients in both PCSK9 inhibitor outcomes studies were permitted to use ezetimibe, very few did. The recommendation placing ezetimibe ahead of PCSK9 inhibitors is primarily due to wide availability as a generic and proven safety and tolerability.
- PCSK9 inhibitors may also be considered in patients with severe primary hypercholesterolemia (e.g., HeFH) with an LDL-C of 100 mg/dL or greater despite maximally tolerated statin and ezetimibe therapy.

HeFH

- National Lipid Association (NLA) treatment guidelines for HeFH recommend targeting a 50% reduction in LDL-C from baseline; however higher risk patients may require a more aggressive treatment goal of less than 100 mg/dL. High risk HeFH patients included those with clinically evident CHD or other atherosclerotic cardiovascular disease, diabetes, a family history of very early CHD (in men < 45 years of age and women < 55

years of age), current smoking, two or more CHD risk factors, or high lipoprotein (a) ≥ 50 mg/dL. Intensification of therapy may also be considered in patients without any of the listed previously factors, if LDL-C remains ≥ 160 mg/dL (or non-HDL cholesterol ≥ 190 mg/dL), or if an initial 50% decrease is LDL-C is not achieved. [13]

- Although treatment targets are recommended by clinical guidelines, they are based primarily on surrogate endpoints, expert opinion, and studies in patients without familial hypercholesterolemia. [13-15]
- NLA guidelines recommend statins as the initial treatment for all patients with FH. Ezetimibe, niacin, and bile acid sequestrants are considered reasonable treatment options for intensification of therapy, or for those intolerant of statins. EAS guidelines for HeFH provide generally similar treatment recommendations but recommend different target LDL levels. [13]

HoFH

- HoFH is a rare, genetic disease characterized by abnormally elevated LDL cholesterol levels and an increased risk for early onset coronary heart disease. LDL levels can range from 300 to over 1000 mg/dL. If not treated, affected patients often die in early adulthood. [16]
- Treatment options include Repatha (evolocumab), Praluent (alirocumab), Juxtapid (lomitapide), traditional lipid-lowering medications, and LDL-apheresis.[16] Kynamro (mipomersen), oligonucleotide inhibitor of apolipoprotein B-100 synthesis indicated for HoFH, was discontinued by its manufacturer in 2018.

Statin intolerance

- ODYSSEY ALTERNATIVE was a 24-week study of Praluent (alirocumab) in patients who were considered to be statin intolerant, which was defined as inability to tolerate at least two statins due to muscle symptoms, with one at the lowest FDA-approved dose. [16]
    * Muscle related symptoms must have begun or increased during statin therapy and stopped when statin therapy was discontinued.
    * The trial included a 4-week, single-blind placebo run-in period, patients who experienced muscle symptoms during the placebo run-in period were excluded. After completion of the run-in period patients were randomized to Praluent (alirocumab), ezetimibe, or atorvastatin.
    * In total, 314 of 361 patients completed the placebo run-in period. Of the 47 placebo run-in failures, 23 (48.9%) reported at least one skeletal muscle-related adverse event.
    * Approximately 70% of patients randomized to atorvastatin completed 24 weeks of the double-blind treatment period. The intent of this arm was to rechallenge patients with a statin.
    * Fewer patients experienced skeletal muscle-related TEAEs in the alirocumab group than the atorvastatin (HR: 0.61; 95% CI: 0.38 to 0.99) or ezetimibe (HR: 0.70; 95% CI: 0.47 to 1.06) groups. Fewer patients in the Praluent (alirocumab) group discontinued the study due to musculoskeletal AEs compared to the atorvastatin group (15.9% versus 22.2%, respectively).

    * Although, this trial was conducted in a "statin intolerant" population, the majority of these patients were able to tolerate statin therapy, thus requiring multiple statin-rechallenges prior to use of a PCSK9 inhibitor is warranted.

- Other studies have also concluded that most patients can tolerate a statin after being re-challenged.
    * In a retrospective analysis of 1,605 statin-intolerant patients conducted by researchers at the Cleveland Clinic, 72.5% of patients were able to tolerate a statin after re-challenge. [17]
    * Authors of a separate retrospective analysis conducted at two academic medical centers concluded that most patients who are rechallenged can tolerate statins long-term. In this study, 92.2% of patients who were re-challenged with a statin were able to continue taking statins after 12-months.
- 2018 AHA/ACC Guidelines state that in patients with statin-associated side effects that are not severe, it is recommended to reassess and to re-challenge to achieve a maximal LDL-C lowering by modified dosing regimen, an alternate statin or in combination with non-statin therapy. Guidelines authors noted that a large majority of patients can tolerate statin re-challenge with an alternative statin or alternative regimen, such as reduced dose or in combination with non-statins.
- The ACC has developed an online application to help providers assess, treat, and manage patients with possible statin intolerance. The tool is available at: http://tools.acc.org/StatinIntolerance/

Dosing considerations

- The recommended starting dose for Praluent (alirocumab) is 75 mg administered subcutaneously once every 2 weeks. If the LDL-C response is inadequate, the dose may be increased to the maximum dose of 150 mg administered every 2 weeks. An alternative starting dose of 300 mg every 4 weeks may also be considered.[3]
- The recommended starting dose of Repatha (evolocumab) for patients with HeFH or clinical ASCVD is 140 mg once every 2 weeks or 420 mg once monthly, administered subcutaneously. The recommended starting dose for patients with HoFH is 420 mg once monthly.[6]
- The recommended dose of Leqvio (inclisiran) is 284 mg given subcutaneously as a single injection, repeated at 3 months, then every 6 months thereafter.[18]

Appendix 1: Dutch Lipid Clinic Network criteria [12]	
Criteria	**Points**
Group 1: family history	
First-degree relative with known premature (less than age 55 for males or 65 for females) coronary heart disease *OR* First-degree relative with known LDL cholesterol above 95th percentile	1
First-degree relative with tendon xanthoma and/or corneal Arcus *OR* Children < 18 years with LDL cholesterol above 95th percentile	2
Group 2: clinical history	
Premature coronary heart disease	2
Subject has cerebral or peripheral vascular disease	1
Group 3: physical examination	
(i) Tendon xanthoma	6
(ii) Corneal arcus in a person before age 45	4
Group 4: biochemical results (LDL-C)	
>8.5 mmol/L (>325 mg/dL)	8
5–8.4 mmol/L (251–325 mg/dL)	5
5.0–6.4 mmol/L (191–250 mg/dL)	3
4.0–4.9 mmol/L (155–190 mg/dL)	1
Group 5: molecular genetic testing (DNA analysis)	
(i) Causative mutation shown in the LDLR, APOB, or PCSK9 genes	8
Scoring	
> 8 points: Definite FH 6-8 points: Probably FH 3-5 points: Possible FH <3 points: Unlikely FH	

Appendix 2: Simon Broome Register Diagnostic Criteria for Definitive FH [19]
Adults: Total cholesterol levels > 290 mg/dL (7.5 mmol/L) or LDL-C > 190 mg/dL (4.9 mmol/L). Children less than 16 years of age: Total cholesterol levels > 260 mg/dL (6.7 mmol/L) or LDL-C > 155 mg/dL (4.0 mmol/L). Plus at least one of the two: **1.** Physical findings: tendon xanthomas or tendon xanthomas in a first or second degree relative. **OR** **2.** DNA-based evidence of an LDL-receptor mutation, familial defective apo B-100, or a PCSK9 mutation.

Appendix 3: Risk Factors for Statin-Associated Muscle Symptoms [1 20]
Hypothyroidism
Multiple or serious co-morbidities, including reduced renal or hepatic function
Rheumatologic disorders such as polymyalgia rheumatica
Steroid myopathy
Vitamin D deficiency
Primary muscle diseases
Acute infection
Organ transplant recipients
Severe trauma
HIV
Diabetes mellitus
Major Surgery
History of creatinine kinase elevation
History of pre-existing/unexplained muscle/joint/tendon pain
Genetic factors such as polymorphisms in genes encoding cytochrome P450 isoenzymes or drug transporter
High level of physical activity
Dietary effects (excessive grapefruit or cranberry juice)
Excess alcohol
Drug abuse (cocaine, amphetamines, heroin)

Appendix 4: Examples of Drug-drug interactions that may increase the risk of skeletal muscle effects with High-Intensity Statins
Strong inhibitors of CYP 3A4 (e.g., clarithromycin, itraconazole, protease inhibitors)
Grapefruit Juice
Cyclosporine
Gemfibrozil and other fibrates
Niacin
Colchicine

Appendix 5: Contraindications to Statin Therapy [10 21]
Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels
History of rhabdomyolysis
Hypersensitivity
Nursing Mothers
Pregnancy

Appendix 6: Clinical Atherosclerotic Cardiovascular Disease (ASCVD) [1]
Acute coronary syndromes
History of coronary or other arterial revascularization
History of myocardial infarction
History of stable or unstable angina
History of stroke or transient ischemic attack (TIA)
Peripheral arterial disease presumed to be of atherosclerotic origin

Appendix 7: Statin Comparison Chart [1]		
% LDL- C Lowering	**Statin Name**	**Strength**
Low-intensity: < 30%	Fluvastatin	20 mg, 40 mg
	Lovastatin	10 mg, 20 mg
	Lovastatin ER (Altoprev)	20 mg
	Pitavastatin (Livalo)	1 mg
	Pravastatin	10 mg, 20 mg
	Simvastatin	5 mg, 10 mg
Moderate-intensity: 31% - 49%	Atorvastatin	10 mg, 20 mg
	Fluvastatin ER (Lescol XL)	80 mg
	Lovastatin	40 mg
	Lovastatin ER (Altoprev)	40 mg, 60 mg
	Pitavastatin (Livalo)	2 mg, 4 mg
	Pravastatin	40 mg, 80 mg
	Rosuvastatin	5 mg, 10 mg
	Simvastatin	20 mg, 40 mg
High-intensity: ≥ 50%	Atorvastatin	40 mg, 80 mg
	Rosuvastatin	20 mg, 40 mg

Appendix 8: AHA/ACC Definition of Very-High Risk ASCVD [1]	
Very high risk includes a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions.	
Major ASCVD Events	**High-Risk Conditions**
Recent ACS (in past 12 months)	Age ≥ 65 years
History of MI (other than recent ACS event)	HeFH
History of ischemic stroke	History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event
Symptomatic Peripheral arterial disease (History of claudication with ABI< 0.85, or previous revascularization or amputation)	Diabetes mellitus
	Hypertension
	Chronic Kidney Disease
	Current Smoking
	Persistently elevated LDL-C (≥ 100 mg/dL) despite maximally tolerated statin therapy and ezetimibe
	History of congestive heart failure

Cross References
Genetic Testing for Familial Hypercholesterolemia, Medical Policy Manual, Policy No. 11
Pharmacy Services Medication Policy Manual, Site of Care Review, dru408

Codes	**Number**	**Description**
HCPCS	J1306	Injection, inclisiran (Leqvio), 1 mg

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Revision History

Revision Date	Revision Summary
3/16/2023	No changes to policy criteria with this annual update.
3/18/2022	New policy (effective 6/1/2022). Replaces individual coverage policies for Praluent (alirocumab), dru406 and Repatha (evolocumab), dru407 and includes Leqvio (inclisiran). No change to intent of coverage from previous criteria: limits coverage to confirmed labeled indications with step therapy with low-cost generics. Inclisiran has an additional clinical step with other PCSK9 inhibitors.

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Medication Policy Manual

Policy No: dru698

Topic: Gene therapies for beta thalassemia

- Casgevy (exagamglogene autotemcel)
- Zynteglo, betibeglogene autotemcel

Date of Origin: April 15, 2022

Committee Approval Date: June 20, 2024

Next Review Date: 2025

Effective Date: September 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Gene therapies in this policy are intravenous (IV) therapies used to treat a rare, genetic blood condition (transfusion dependent beta thalassemia).

PLEASE NOTE:

This policy does not apply to Casgevy (exagamglogene autotemcel) for use in sickle cell disease (SCD). Please refer to policy dru766 gene therapies for sickle cell disease for coverage details.

Policy/Criteria

Most contracts require pre-authorization of gene therapies for beta thalassemia prior to coverage.

I. Gene therapies for beta thalassemia are considered investigational, except for those situations specifically addressed in the policy criteria below.

PLEASE NOTE: Under this criterion, any products not specifically addressed in this policy will be considered investigational.

II. Continuation of therapy (COT): Gene therapies for beta thalassemia may be considered medically necessary for COT when full policy criteria below are met, including quantity limit. However, gene therapies for beta thalassemia are not coverable for repeated doses and are not coverable if a patient has previously received prior gene therapy for SCD.

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment naïve): Gene therapies for beta thalassemia may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A and B below are met.

A. A diagnosis of **transfusion-dependent beta-thalassemia** (TDT) when there is clinical documentation that all criteria (1 through 6) below are met:

1. The diagnosis of beta thalassemia is genetically confirmed.

AND

2. No prior hematopoietic stem cell transplantation (HSCT).

AND

3. Documented transfusion-dependence, defined as transfusion of at least 8 red blood cell transfusions (RBCTs) in the prior 12-month period.

AND

4. Standard transfusion therapy (RBCTs) **and** iron chelation therapy (ICT) have been ineffective, not tolerated, or use is contraindicated (as defined in A*ppendix 2*).

AND

5. ***For Casgevy (exagamglogene autotemcel) only:*** The patient is 12 years of age or older at the time of infusion.

AND

6. ***For Zynteglo (betibeglogene autotemcel) only:*** The patient is 4 years of age or older at the time of infusion.

AND

B. The patient is a suitable candidate for gene therapies for beta thalassemia and meets all of the following criteria (1, 2, and 3) below:

1. No prior use of gene therapy (see *Appendix 1*).

AND

2. Patient is fit for therapy, as defined by meeting all the criteria (a, b, and c) below.

a. The patient has a Karnofsky or Lansky performance status (KPS) of at least 80 [or ECOG performance status of 0 or 1; the patient is ambulatory and able to carry out work of a light or sedentary nature].

AND

b. The patient has adequate and stable kidney, liver, and cardiac function (provider attestation).

AND

c. The patient has no active systemic infections (including, but not limited to HCV, HBV, and HIV infection) (provider attestation).

AND

3. Treatment with HSCT is contraindicated (including, but not limited to lack of a matched donor, comorbidities, and age).

PLEASE NOTE: Suitability for gene therapy must be documented in recent clinical documentation (such as in chart notes, laboratory reports), which MUST include evaluation for HSCT [bone marrow transplant (BMT)].

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers gene therapies for beta thalassemia coverable only under the medical benefit (as provider-administered medications).

B. When pre-authorization is approved, gene therapies for beta thalassemia may be authorized in quantities of one treatment course per lifetime.

C. Additional infusions of gene therapies for beta thalassemia will not be authorized.

IV. Gene therapies for beta thalassemia are considered investigational when used for all other conditions, including, but not limited to:

A. Alpha thalassemia

B. N**on**-transfusion dependent beta thalassemia

C. ***Zynteglo (betibeglogene autotemcel) only:*** Sickle cell disease (SCD).

Position Statement

Summary

- Gene therapies for beta thalassemia are ex-vivo therapies given as a one-time IV infusion.
- FDA approved products include the following:
  - Casgevy (exagamglogene autotemcel), a novel clustered regularly interspaced short palindromic repeats **(**CRISPR) and Cas9 gene-editing cell therapy that targets BCL11A gene to increase production of fetal Hb.
  - Zynteglo (betibeglogene autotemcel) uses a lentiviral vector to encode a functional copy of a modified ß-globin gene into hematopoietic stem cells.
- Gene therapies for beta thalassemia are complex, high-cost treatments that require several phases of administration, extended hospitalization, and extensive supportive care, similar to a hematopoietic stem cell transplantation (HSCT).
- The intent of this policy is to allow for coverage of gene therapies for beta thalassemia for the indication and dose for which it has been shown to be safe and effective in clinical trials. This includes for treatment of genetically confirmed transfusion-dependent beta-thalassemia (TDT). Aside from transfusion-dependence, patients must be clinically suitable to receive gene therapies for beta thalassemia.
- Current available evidence for gene therapies for beta thalassemia is limited to small, single-arm, non-randomized trials that evaluated transfusion independence as the primary endpoint.
  - Based on most recent data analyses of the pivotal trials for Casgevy and Zynteglo, the majority of patients were transfusion free for a year or more.
  - However, the long-term impact of these gene therapies for beta thalassemia on other clinically relevant outcomes, such as overall survival (OS), is currently unknown.
- Standard of care therapies, including transfusions along with iron chelation therapy (ICT) and HSCT, have proven survival benefit in patients with TDT. However, not all patients with TDT are able to tolerate iron overload-associated adverse events, despite hematologic response from transfusions. In addition, many patients with TDT do not have an HLA-matched donor for HSCT or are not suitable candidates for HSCT. For these specific populations, the potential benefit of these gene therapies for beta thalassemia may outweigh the risks.
- Currently, there is insufficient evidence to establish the safety and efficacy in other settings, including non-transfusion dependent beta thalassemia or alpha thalassemia.
- Gene therapies for beta thalassemia may be covered for up to one dose per lifetime. There is no data on the safety or efficacy of repeated doses.

Disease Background [1]

- Beta thalassemia is a rare, recessive genetic blood disease caused by a mutation in the ß-globulin gene. It is characterized by an absence or reduced production of ß-globin, an integral component of hemoglobin (Hgb).

    - Hemoglobin A (HgbA), the most common form of adult hemoglobin, consists of a tetramer containing alpha (α) and beta (ß)-globin subunits.
    - Under normal physiologic conditions, the α/ß-globin chain ratio is tightly regulated. However, the absence or reduction in ß-globin chains that occurs in beta thalassemia leads to an imbalance in this ratio. This leads to an increase in unbound non-soluble α-globin chains, which causes cellular damage.
- Ineffective erythropoiesis is a hallmark of beta-thalassemia, which leads to anemia and a number of subsequent pathophysiologic complications: hemolysis, hypercoagulability, iron overload, extramedullary hematopoiesis, heart disease, and hepatic cirrhosis.
- Symptoms of beta thalassemia include fatigue, weakness, poor appetite, pallor, jaundice, growth retardation, delayed puberty, abdominal swelling, and bone problems (especially facial bone deformities).

Clinical Efficacy

Zynteglo (betibeglogene autotemcel) in Transfusion Dependent Beta Thalassemia (TDT)

- The safety and efficacy of Zynteglo (betibeglogene autotemcel) was established primarily on four small, single-arm, non-randomized trials in patients with TDT. All four trials evaluated transfusion independence (TI). [2 3]
    - All patients had genetically confirmed TDT and transfusion-dependence, defined as required ≥ 8 RBCTs per year. In addition, all were ≤ 50 years of age and fit for Zynteglo (betibeglogene autotemcel) therapy (Karnofsky or Lansky performance status ≥ 80, adequate organ function, and no active infections, clinically stable and eligible for a HSCT but without an HLA-matched donor). Patients with severe liver dysfunction or significant cardiac abnormalities (with myocardial iron stores of T2 < 10 msecs) were excluded from trial enrollment.
    - TI, the primary endpoint, was defined as a weighted average Hgb ≥ 9 g/dl without any RBCTs for a continuous period of at least12 months.
    - The initial trials (Northstar and HGB-205) enrolled both non-ß^0/ß^0 TDT (n= 13) and ß^0/ß^0 TDT (n=9) patients.
        - The majority of patients with non-ß^0/ß^0 TDT achieved TI [92% (12/13)], whereas only one-third of the patients with ß^0/ß^0 TDT achieved TI [33% (3/9)].
        - Given the low response in patients with ß^0/ß^0 TDT, the subsequent trial (Northstar-2) of Zynteglo (betibeglogene autotemcel) only investigated use for non-ß^0/ß^0 TDT.
        - In addition, after this trial, the Zynteglo (betibeglogene autotemcel) was reformulated with a modified manufacturing process to improve the levels of gene therapy derived HgbA (increased viral vector copy number).
    - The subsequent Northstar-2 trial enrolled patients with non-ß0/ß0 TDT (n=23).
        - At the time of the data cut, 92% of patients achieved TI, over the average follow up time of approximately two years.

- Of note, this trial used the updated formulation of Zynteglo (betibeglogene autotemcel).
- Additional follow up data is pending (expected after February 2024), to evaluate the durability and long-term safety of Zynteglo (betibeglogene autotemcel).

* Most recently, the Northstar-3 trial enrolled patients with TDT that had both ß0/ß0 TDT and non-ß0/ß0 TDT (n=18). The trial reported similar results to the prior trials, with efficacy across both genotypes.[4]
  - At the completion of the trial, 88.9% of patients achieved TI, over the average follow up time of two years.
  - Of note, 12 of the 18 patients (66%) were ß0/ß0 TDT, while only 6 (33%) were non-ß0/ß0 TDT.
* Similar to a HSCT, patients undergo myeloablative chemotherapy prior to Zynteglo (betibeglogene autotemcel) infusion, requiring on average ≥ 30 days of inpatient hospitalization post infusion of Zynteglo (betibeglogene autotemcel)

<u>Casgevy (exagamglogene autotemcel) in TDT</u>

- The safety and efficacy of Casgevy (exagamglogene autotemcel) was established primarily from the ongoing CLIMB THAL-111 study (n=52), a small phase 2/3, non-randomized, open-label, single arm trial in patients with genetically confirmed TDT (ß0/ß0 TDT and non-ß0/ß0 TDT). The trial evaluated transfusion independence (TI). [5-8]
  * Patients were aged 12 to 35, with genetically confirmed beta thalassemia that was transfusion-dependent (defined as either 10 units or RBCTs per year or 100 ml/kg/year of RBCTs in the previous two years), with the average patient enrolled receiving 35 units of RBCTs per year.
  * All patients were fit for Casgevy (exagamglogene autotemcel) therapy, defined as having a Karnofsky or Lansky performance status ≥ 80, adequate organ function, no active infections, clinically stable, and eligible for a HSCT but without an HLA-matched donor. Patients with severe liver, renal, or cardiac dysfunction and those with a prior HSCT were excluded from trial enrollment.
  * The trial enrolled of both ß0/ß0 and non-ß0/ß0 genotypes, with 31 patients (60%) having ß0/ß0 genotype and 21 patients (40%) having non-ß0/ß0 genotypes.
  * The primary endpoint was the number of patients achieving TI for 12 consecutive months while maintaining a Hgb ≥ 9 g/dl.
  * At the most recent available data cut-off (Jan 2023), 32 of the 35 eligible patients for the primary endpoint achieved TI for 12 consecutive months (91.4%, P<0.0001), with the mean duration of effect of 21 months. Efficacy was seen across both genotypes.
  * Patients undergo myeloablative conditioning prior to Casgevy (exagamglogene autotemcel) infusion, with patients requiring on average ≥ 30 days of inpatient hospitalization from conditioning to discharge.
  * Additional follow up data is pending (expected after February 2024), further evaluating the durability and safety of Casgevy (exagamglogene autotemcel) in TDT.

Clinical Guidelines/Standard of Care Treatment [1 9]

- The treatment of patients with transfusion-dependent beta-thalassemia requires a multidisciplinary approach due to the number of complications associated with the disease.
- Current treatment approaches for patients with beta-thalassemia mainly address the anemia-related symptoms of the disease. The key components of symptomatic care are RBCTs and HSCT (for patients with an HLA-matched donor that are clinically eligible).
- Currently, HSCT is the only proven cure for beta-thalassemia, with greatest benefit seen in young patients. However, use of HSCT is limited by availability of HLA-matched donors for the stem cell donation and the clinical stability of the patient being treated (e.g., adequate organ function, comorbidities, age).
- Patients with transfusion-dependent beta-thalassemia require regular transfusions (every 2 to 5 weeks) to maintain an acceptable Hgb. Recommended pre-transfusion Hgb target is 9.0 to 10.5 g/dl to promote normal growth, allow normal physical activities, and suppress bone marrow activity. A higher pre-transfusion Hgb target of 11 to 12 g/dl is recommended for some patients who develop disease complications (e.g., cardiac disease).
- Disease management with RBCTs and HSCT has greatly improved survival in patients with severe forms of beta-thalassemia, However, iron overload-related comorbidities can arise due to frequent RBCTs. This mainly affects the heart, liver, and endocrine organ systems.
    * Without an effective iron chelation therapy (ICT) regimen, uncontrolled iron overload increases the risks of heart failure, endocrine damage, liver cirrhosis, and hepatocellular carcinoma.
    * Cardiac complications cause the majority (~70%) of deaths in patients with TDT.
- Iron overload is managed with life-long ICT. ICT with deferoxamine, deferasirox, or deferiprone is titrated to iron levels, in the liver, heart, and blood, as follows:
    * Liver iron concentration (LIC) 2-5mg/g of dry weight
    * Myocardial iron: T2 >20 msecs
    * Serum ferritin < 1000 ng/ml

Safety [2 3]

- The most common grade ≥ 3 treatment-emergent adverse events (AEs) seen during pivotal trials were thrombocytopenia, neutropenia, anemia, leukopenia, febrile neutropenia, epistaxis, pyrexia, decreased appetite, and hepatic veno-occlusive disease.
- Of note, the AEs noted above are consistent with those typically seen with the conditioning regimen used prior to infusion with gene therapies for beta thalassemia.
- Long-term safety data is limited as these trials are of a small sample size and short duration for a chronic disease.
- Additional safety data is needed to establish potential long-term toxicities that may be associated with these gene therapies for beta thalassemia, including the risk for malignancies or off target mutations.

Appendix 1:

Gene Therapies [a]
- Casgevy (exagamglogene autotemcel) - Lyfgenia (lovotibeglogene autotemcel) - Zynteglo (betibeglogene autotemcel) - Chimeric Antigen Receptor (CAR) T-cell Therapies (see dru523) - Roctavian (valoctocogene roxaparvovec) - Hemgenix (etranacogene dezaparvovec)

[a] Including, but not limited to these gene therapies

Appendix 2:

Definition of Ineffective/Not tolerated/contraindications to Standard TDT Therapy [transfusion and/or iron chelation therapy (ICT)] [1]

- Patient is unable to maintain pre-transfusional Hgb goal.
- Transfusion-related iron overload, despite compliant use of ICT. [a]
- Patient intolerant of ICT or has a documented contraindication to all ICT options.
- Patient intolerant of RBCTs, such as:
  * Transfusion reactions (allergic, hemolytic, alloimmunization), despite management by a Transfusion Medicine specialist.
  * Excessive volume overload, such that RBCTs are not an option.
  * Other: Transfusion-related lung injury (TRALI), transfusion-related GVHD.
- Clinical or laboratory documentation of persistent ineffective erythropoiesis, despite RBCTs. Clinical signs include facial bone changes (frontal bossing and maxillary hyperplasia), poor growth, symptomatic extramedullary hematopoiesis, fatigue and reduced physical functioning.

[a] Liver iron concentration (LIC) > 5mg/g, myocardial iron (T2) >20 msecs, serum ferritin ≥ 1000 ng/ml

Cross References
Chimeric Antigen Receptor (CAR) T-cell Therapies, Medication Policy Manual, Policy No. dru523
Roctavian, valoctocogene roxaparvovec, Medication Policy Manual, Policy No. dru641
Gene therapies for hemophilia B, Medication Policy Manual, Policy No. dru735
Gene therapies for sickle cell disease, Medication Policy Manual, Policy No. dru766

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Revision History

Revision Date	Revision Summary
6/20/2024	Updated cross references, no criteria changes with this annual review
3/21/2024	• Renamed policy 'Gene therapies for beta thalassemia'. • Added Casgevy (exagamglogene autotemcel). • Updated criteria as follows: - Added age criteria for each product. - Updated diagnostic criteria to include both beta thalassemia genotypes (β^0/β^0 TDT and non-β^0/β^0 TDT). - Reworded HSCT evaluation criteria to specify no contraindications.
6/15/2023	No criteria changes with this annual update.
9/23/2022	Updated policy to show new brand name of Zynteglo (betibeglogene autotemcel).
3/18/2022	New policy (effective 6/1/2022). Limits use to TDT patients with non-β^0/β^0 genotype that have failed standard transfusion/iron chelation therapy, for whom a hematopoietic stem cell transplantation (HSCT) is appropriate, but a matched donor is not available.

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Medication Policy Manual	**Policy No:** dru700
Topic: Fyarro, nab-sirolimus, protein-bound sirolimus	**Date of Origin:** July 15, 2022
Committee Approval Date: September 19, 2024	**Next Review Date:** 2025
Effective Date: December 1, 2024	

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Fyarro (nab-sirolimus, protein-bound sirolimus) is an intravenously administered formulation of sirolimus approved for use in patients with a specific type of tumor [malignant perivascular epithelioid cell tumors (PEComas)].

Policy/Criteria

Most contracts require pre-authorization approval of Fyarro (nab-sirolimus) prior to coverage.

I. Continuation of therapy (COT): Fyarro (nab-sirolimus) may be considered medically necessary for COT when full policy criteria below are met, including quantity limits.

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan*

II. New starts (treatment-naïve patients): Fyarro (nab-sirolimus) is considered not medically necessary for malignant **perivascular epithelioid cell tumor** (PEComa).

III. Fyarro (nab-sirolimus) is considered investigational when used for all other conditions.

IV. Administration, Quantity Limitations, and Authorization Period

- **A.** Regence Pharmacy Services considers Fyarro (nab-sirolimus) coverable only under the medical benefit (as a provider-administered medication).
- **B.** Although the use of Fyarro (nab-sirolimus) is considered "not medically necessary," if pre-authorization is approved, Fyarro (nab-sirolimus) will be authorized in quantities of up to two, 100mg/m^2 infusions every 21 days until disease progression.
- **C.** Authorization **shall** be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

Position Statement

Summary

- Fyarro (nab-sirolimus), a mechanistic target of rapamycin (mTOR) inhibitor, is considered 'not medically necessary' for locally advanced or metastatic malignant perivascular epithelioid cell tumor (PEComa) as it has no proven benefit over much less costly mTOR inhibitor alternatives.
- Fyarro (nab-sirolimus) is a new formulation of sirolimus in which a sirolimus molecule is bound to albumin, a protein found in the blood stream. This alters the pharmacokinetics of sirolimus in the body; however, the clinical relevance of this has not been determined.
- Sirolimus has been available for many years. It is available as an oral tablet and as an injectable prodrug, temsirolimus, which is converted to sirolimus once infused into the body. Both of these products are available as significantly less-costly generics.
- Fyarro (nab-sirolimus) was approved for malignant PEComa based on a small, uncontrolled (it was not directly compared to any other therapy), observational study that looked at the change in tumor size on x-ray as a surrogate endpoint (low quality evidence). The study found that tumors slowed in growth or decreased in size in some patients who received Fyarro (nab-sirolimus). However, this tumor response has not been shown to predict improved survival or improve symptom control, clinically important outcomes in patients with malignant PEComa.
- Other mTOR inhibitors have been used 'off-label' to manage malignant PEComa including oral sirolimus, intravenous temsirolimus, and oral everolimus. The available evidence for these drugs in malignant PEComa is also of low quality. It is based on case studies which also evaluated change in tumor size on x-ray as a surrogate endpoint. As was observed with Fyarro (nab-sirolimus) some patients receiving these medications had slowed growth or decrease in size of their tumors.
- The side effects experienced with Fyarro (nab-sirolimus) are similar to those experienced with other mTOR inhibitors. Because Fyarro (nab-sirolimus) has not been directly compared with other mTOR inhibitors, marketing claims that it may be safer or more effective than other sirolimus formulations cannot be substantiated.
- The National Comprehensive Cancer Network (NCCN) soft tissue sarcoma (STS) guideline lists Fyarro (nab-sirolimus), oral sirolimus, temsirolimus, and everolimus as potential therapies for malignant PEComa.
- Fyarro (nab-paclitaxel) is administered intravenously on days 1 and 8 of each 21-day cycle in a dose of 100 mg/m^2. It is administered until disease progression or unacceptable toxicity.
- The safety and effectiveness of Fyarro (nab-paclitaxel) for conditions other than malignant PEComa has not been studied.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Product Description [1]

- Fyarro (nab-sirolimus) is a new formulation of sirolimus, an mTOR inhibitor, in which a sirolimus molecule is attached to albumin. This alters the pharmacokinetics of sirolimus in the body; however, the clinical relevance of this has not been determined.
- Sirolimus is also available as an oral tablet, and as an injectable prodrug of sirolimus, temsirolimus. Both of these products have been around for many years and are currently available as significantly less-costly generics.

Clinical Efficacy

- Fyarro (nab-sirolimus) was evaluated in a small, non-comparative, observational trial (low quality evidence) in patients with malignant peri-vascular epithelioid cell tumor (PEComa). [2]
    * Patients in the trial had locally advanced (ineligible for surgical resection) or metastatic malignant PEComa.
    * Patients with lymphangioleiomyomatosis (LAM), a specific subtype of PEComa, were excluded from the trial.
    * Patients who received prior therapy with an mTOR inhibitor were also excluded from the trial because resistance to this class of drugs may occur over time.
    * The study evaluated tumor response, a radiographic measure of the size of a tumor, as a surrogate endpoint. Some patients in the study had stabilization or reduction in the size of their tumors while on Fyarro (nab-sirolimus). However, tumor response has not been shown to accurately predict benefit with regard to any clinically relevant outcome such as improved survival or symptom control.

- Other sirolimus formulations (oral sirolimus, intravenous temsirolimus), as well as everolimus (another mTOR inhibitor), have been used 'off-label' for treating malignant PEComa. Tumor responses have also been observed with these drugs. Like the evidence for Fyarro (nab-sirolimus) this is also considered to be low quality evidence. [3-6]
- None of the mTOR inhibitors have been directly compared with one another so it is not known if there are any differences in safety or effectiveness among the various products. Furthermore, the generic mTOR products are less costly so provide better value. For this reason, Fyarro (nab-sirolimus) is considered not medically necessary.

Guidelines [6]

- The National Comprehensive Cancer Network (NCCN) soft tissue sarcoma (STS) guideline lists Fyarro (nab-sirolimus), oral sirolimus, temsirolimus, and everolimus as potential therapies for malignant PEComa.

Investigational Uses *[7,8]*

- Fyarro (nab-sirolimus) has not been studied in any condition other than malignant PEComa.
- The NCCN compendium does not list any additional uses for the Fyarro formulation of sirolimus (nab-sirolimus).

Safety *[1,9,10]*

- Common adverse effects (AEs) observed with administration of mTOR inhibitors include stomatitis, rash, gastrointestinal symptoms, infection, and edema.
- There are no studies directly comparing the safety of different mTOR inhibitors with one another, so it is not known whether any one product is better tolerated than another.

Dosing *[1]*

- Fyarro (nab-paclitaxel) is administered intravenously on days 1 and 8 of each 21-day cycle in a dose of 100 mg/m^2. It is administered until disease progression or unacceptable toxicity.
- Dose modifications are made for certain AEs including stomatitis, anemia, thrombocytopenia, neutropenia, infections, hypokalemia, hyperglycemia, interstitial lung disease, and hemorrhage.

Codes	Number	Description
HCPCS	C9091	Sirolimus Protein-Bound Particles for Injectable Suspension (Albumin-Bound), for Intravenous Use (Fyarro)
HCPCS	J9331	Injection, sirolimus protein bound particles, 1 mg

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Revision History

Revision Date	Revision Summary
9/19/2024	No criteria changes with this annual review.
9/14/2023	No criteria changes with this annual review.
9/23/2022	No changes to coverage criteria with this annual update.
06/17/2022	New Policy (effective 7/15/2022). - The use of Fyarro (nab-sirolimus) for malignant PEComa is considered Not Medically Necessary - All other uses are considered investigational

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Medication Policy Manual | **Policy No:** dru701

Topic: Kimmtrak, tebentafusp-tebn | **Date of Origin:** July 15, 2022

Committee Approval Date: June 20, 2024 | **Next Review Date:** 2025

Effective Date: September 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Kimmtrak (tebentafusp-tebn) is an intravenously administered immunotherapy approved for use in patients with a specific type of cancer (HLA-A*02:01-positive, advanced uveal melanoma).

Policy/Criteria

Most contracts require pre-authorization approval of Kimmtrak (tebentafusp-tebn) prior to coverage.

I. Continuation of therapy (COT): Kimmtrak (tebentafusp-tebn) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan*

II. New starts (treatment-naïve patients): Kimmtrak (tebentafusp-tebn) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A, B, and C below are met:

A. A diagnosis of **uveal melanoma**, unresectable or metastatic.

AND

B. The patient is Human Leukocyte Antigen (HLA)-A*02:01-positive.

AND

C. Kimmtrak (tebentafusp-tebn) will be used as monotherapy.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Kimmtrak (tebentafusp-tebn) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Kimmtrak (tebentafusp-tebn) may be approved for up to four, 68 mcg infusions per month until disease progression.

C. Authorization **may** be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, including disease stability or improvement relative to baseline symptoms.

IV. Kimmtrak (tebentafusp-tebn) is considered investigational when used for all other conditions, including but not limited to cutaneous melanoma.

Position Statement

Summary

- Kimmtrak (tebentafusp-tebn) is an intravenously administered immunotherapy. It binds to the human leukocyte antigen (HLA)-A*02:01/gp100 complex on the surface of uveal melanoma tumor cells. This helps the bodies T cells recognize, attack, and kill the tumor cells.
- The intent of this policy is to allow coverage of Kimmtrak (tebentafusp-tebn) in the clinical setting described in the coverage criteria above, where it has been evaluated for efficacy, up to the dose shown to be safe in clinical trials.
- The FDA approval of Kimmtrak (tebentafusp-tebn) was based on one trial in HLA-A*02:01-positive adult patients with metastatic uveal melanoma. Patients enrolled in the trial had no prior systemic therapy or liver-directed therapy for their metastatic disease. Kimmtrak (tebentafusp-tebn), administered as monotherapy, was found to improve overall survival (OS) relative to physician's choice of guideline-recommended therapies. OS is a meaningful clinical outcome in metastatic uveal melanoma which has no cure and is associated with high morbidity and mortality.
- In general, therapies used to treat cutaneous melanoma do not work very well in uveal melanoma due to differences in molecular markers and biology.
- The National Comprehensive Cancer Network (NCCN) uveal melanoma guideline lists Kimmtrak (tebentafusp-tebn) as an option for patients with distant metastatic disease who are HLA A*02:01-postive. For metastases confined to the liver, the guideline recommends considering front-line use of liver-directed palliation for symptomatic patients.
- Kimmtrak (tebentafusp-tebn) may be covered in doses of up to 68 mcg each week, the dose studied in the pivotal trial, until disease progression. The safety and effectiveness of higher doses have not been established.
- The safety and effectiveness of Kimmtrak (tebentafusp-tebn) in other conditions have not been established. This includes metastatic cutaneous melanoma where Kimmtrak (tebentafusp-tebn) has not been formally evaluated.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy

- The efficacy of Kimmtrak (tebentafusp-tebn) was studied in a fair quality, open-label, randomized controlled trial in HLA-A*02:01-positive patients with metastatic uveal melanoma. The trial evaluated overall survival (OS) in patients receiving Kimmtrak (tebentafusp-tebn) relative to those receiving Physician's choice of therapy. [1,2]
    * The patients in the trial had no previous systemic or liver-directed therapy for their metastatic disease; however, prior neoadjuvant or adjuvant therapy for early-stage disease was allowed.
    * Patients received either single-agent Kimmtrak (tebentafusp-tebn) or Physician's choice of one of the following three therapies: pembrolizumab (Keytruda), ipilimumab (Yervoy), or dacarbazine. Most patients (82%) received pembrolizumab (Keytruda) in the Physician's choice treatment arm. *(Note: Each of the three therapies included in the comparator arm is included in the current NCCN guideline as a potential therapy for metastatic uveal melanoma)*
    * Treatment was continued until radiographic disease progression. Subsequent therapy was determined at the investigator's discretion.
- The median OS was 21.7 months and 16.0 months in the Kimmtrak (tebentafusp-tebn) and Physician's choice treatment arms, respectively. [1,2] This difference is both statistically and clinically relevant. OS is a clinical outcome of importance in patients with metastatic uveal melanoma, an incurable disease with high morbidity and mortality.
- Note: The pivotal trial excluded patients who had prior liver-directed therapy so it would be unknown if the survival benefit associated with Kimmtrak (tebentafusp-tebn) would extend to this population.

Guideline recommendations [3]

- The current National Comprehensive Cancer Network (NCCN) uveal melanoma guideline lists a clinical trial as the preferred recommendation for patients with metastatic uveal melanoma indicating the lack of a well-defined standard of care in this disease.
- For patients with distant metastatic disease who are HLA A*02:01-postive, Kimmtrak (tebentafusp-tebn) is listed as a treatment option. If metastases are confined to the liver, the guideline recommends considering front-line use of liver-directed palliation for patients who are symptomatic.
- Other recommended therapies for uveal melanoma include medications typically used in the treatment of cutaneous melanoma (e.g., immune checkpoint inhibitors, and cytotoxic chemotherapy). However, the efficacy of these therapies in uveal melanoma is poor due to the differences in molecular markers and biology of these two types of tumors.

Investigational Uses [4]

- There is interest in using Kimmtrak (tebentafusp-tebn) in metastatic cutaneous melanoma in combination with other immunotherapies; however, there are currently no well-controlled, published trials supporting its safety and efficacy in this population.
- There is no evidence to support the use of Kimmtrak (tebentafusp-tebn) in combination with any other therapy in uveal melanoma, or any other condition.
- No studies (enrolling or ongoing) were identified for Kimmtrak (tebentafusp-tebn) outside of the melanoma setting.

Safety [2,5]

- There is a Boxed Warning for Kimmtrak (tebentafusp-tebn) describing the potential for cytokine release syndrome (CRS) when initiating therapy.
- Approximately one in three to four patients who received Kimmtrak (tebentafusp-tebn) in the pivotal trial experienced a dose reduction, interruption, or permanent discontinuation.

Dosing [5]

- Kimmtrak (tebentafusp-tebn) is intravenously administered each week until disease progression.
- The dose of Kimmtrak (tebentafusp-tebn) is slowly increased to minimize the risks of hypotension during/after infusion. The initial three doses should be administered in an appropriate setting where the patient can be monitored for at least 16 hours following infusion. Once it is established that the patient is tolerating the medication, subsequent doses can be given in an appropriate ambulatory care setting.

Cross References
Keytruda, pembrolizumab, Medication Policy Manual, Policy No. dru367
Opdivo, nivolumab, Medication Policy Manual, Policy No. dru390
Yervoy, ipilimumab, Medication Policy Manual, Policy No. dru238
Mitogen-activated extracellular signal-regulated kinase (MEK) Inhibitors, Medication Policy Manual, Policy No. dru727
BRAF inhibitors, Medication Policy Manual, Policy No. dru728

Codes	Number	Description
HCPCS	J9274	Tebentafusp-tebn (Kimmtrak) Injection, for Intravenous Use

References

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Revision History

Revision Date	Revision Summary
6/20/2024	No criteria changes with this annual review.
9/14/2023	No criteria changes with this annual review.
06/17/2022	New Policy (effective 7/15/2022). • Limits coverage to HLA-A*02:01-positive patients with unresectable or metastatic uveal melanoma when Kimmtrak (tebentafusp-tebn) is given as monotherapy. • Kimmtrak (tebentafusp-tebn) may be covered in doses up to 68 mcg weekly, the dose studied in the pivotal trial and the maximum dose listed in the FDA label.

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Medication Policy Manual | **Policy No:** dru702

Topic: Xipere, triamcinolone acetonide injectable suspension for suprachoroidal use | **Date of Origin:** April 15, 2022

Committee Approval Date: March 21, 2024 | **Next Review Date:** 2025

Effective Date: June 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Xipere (triamcinolone acetonide injectable suspension for suprachoroidal use) is a steroid that is injected directly into the eye (suprachoroidal) to help improve swelling associated with specific eye conditions (as detailed below in the coverage criteria).

PLEASE NOTE: Triesence (triamcinolone acetonide injectable suspension for periocular/ intravitreal use) is available without pre-authorization.

Policy/Criteria

Most contracts require pre-authorization approval of Xipere (triamcinolone acetonide injectable suspension for suprachoroidal use) prior to coverage.

I. Continuation of therapy (COT): Xipere (triamcinolone acetonide injectable suspension for suprachoroidal use) may be considered medically necessary for COT when full policy criteria below are met.

Please note: *Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Xipere (triamcinolone acetonide injectable suspension for suprachoroidal use) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) confirming that treatment with topical, oral, AND injectable (periocular or intravitreal) corticosteroids (as listed in *Table 1*) has been:

A. Ineffective after two weeks of therapy.

OR

B. Not tolerated.

OR

C. Use to all forms is documented as medically contraindicated.

TABLE 1.

Lower-Cost Corticosteroid Step Therapy
Topical ophthalmic corticosteroids (variable dose, based on formulation)
Oral corticosteroids (such prednisone ≥ 20 mg/day or equivalent for at least 2-4 weeks)
Triesence (triamcinolone acetonide injectable), intravitreal OR Periocular (such as subconjunctival, subtenon, suprachoroidal, or peribulbar)

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Xipere (triamcinolone acetonide injectable suspension for suprachoroidal use) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Xipere (triamcinolone acetonide injectable suspension for suprachoroidal use) will be authorized in quantities up to two of the 40 mg/1mL vials in 24 weeks (based on a dose of 4 mg/0.1 mL every 12 weeks).

C. Authorization shall be reviewed at least every 24 weeks (six months). Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, including disease stability or improvement relative to baseline symptoms.

IV. Xipere (triamcinolone acetonide injectable suspension for suprachoroidal use) is considered investigational when:

A. Used for any route of administration other than suprachoroidal.

B. Used concomitantly with any other long-acting ophthalmic corticosteroid formulations, such as Ozurdex (dexamethasone implant) or fluocinonide (Retisert, Iluvien, Yutiq) (see *Appendix 1*).

Position Statement

Summary

- Xipere (triamcinolone acetonide injectable suspension for suprachoroidal use) ["Xipere (triamcinolone acetonide suprachoroidal)"] is a corticosteroid injected directly into the suprachoroidal space of the eye that has been studied and approved to reduce the macular edema associated with uveitis.
- The intent of the policy is to allow for coverage of Xipere (triamcinolone acetonide suprachoroidal) when all the best value steroids, including topical ophthalmics, oral, and periocularly/intravitreally injectables, are not an option.
- There is no evidence that Xipere (triamcinolone acetonide suprachoroidal) is safer or more effective than lower-cost steroids, including Triesence (triamcinolone acetonide injectable suspension for periocular/intravitreal use).
- However, Xipere (triamcinolone acetonide suprachoroidal) is significantly more costly than various lower-cost steroids, including triamcinolone acetonide periocular/ intravitreal (Triesence). Therefore, the use of Xipere (triamcinolone acetonide suprachoroidal) is considered necessary only when all lower cost steroid treatment options are ineffective, not tolerated, or documented as medically contraindicated.
- As a class, corticosteroids are associated with several adverse events (AEs). Ocular AEs include elevation in intraocular pressure (IOP), glaucoma, and formation of cataracts.
- Xipere (triamcinolone acetonide suprachoroidal) may be covered for up to a 4 mg dose, the dose studied in clinical trials. The safety and effectiveness of higher doses have not been established. The dose may be repeated, if clinically indicated, after 12 weeks.

Background

- There are many formulations of corticosteroids for treatment of uveitis, including but not limited to: [1]
  * Topical ophthalmic: dexamethasone, prednisolone, available as solutions, suspensions, gels, and/or ointments.

    * Oral steroids: prednisone, dexamethasone, methylprednisolone, prednisolone
    * Periocular/intravitreal injection: triamcinolone acetonide (Triesence; Kenalog periocular only)
    * Ocular steroid implants: Ozurdex (dexamethasone implant), fluocinonide (Retisert, Iluvien, Yutiq)

- The use of steroids for ocular inflammatory diseases, including non-infectious uveitis, is considered a mainstay of therapy. Ocular inflammation is managed with a stepwise approach.[2-4]
    * Topical steroids +/- a topical non-steroidal anti-inflammatory (NSAID) as usual initial therapy. Patients with posterior uveitis, including panuveitis, are less likely to respond to topical steroids.
    * If additional acute inflammation control is needed, systemic steroids (such as oral prednisone) may be added. Guidelines recommend a high dose course (prednisone 1 mg/kg/day or up to 60-80 mg per day) for up to one month.
    * Regional administration of steroids (such as triamcinolone injection) may be used to maximize local ocular benefit and minimize systemic steroid exposure and associated adverse events. Steroids are injected periocularly (subconjunctival, subtenon, suprachoroidal, orbital floor, or peribulbar) or intravitreally, dependent on the type and location of the inflammation.
    * A systemic immunomodulator (csDMARD, such as mycophenolate mofetil, azathioprine, methotrexate, cyclosporine, or tacrolimus) may be used if there is no response, or worsening, after two to four weeks of oral steroids (e.g., prednisone ≥ 30mg/day or 0.5 mg/kg/day). Initiation of therapy is dependent on several factors, including underlying etiology and severity of the inflammation.
- There are existing formulations of triamcinolone acetonide injection for ocular inflammatory conditions, given inside the eye (intraocular, intravitreal) or around the eye (periorbital, periocular). [3,5,6]
    * Triesence (triamcinolone acetonide injection) has many years of experience to establish the safety and efficacy for intravitreal use.
    * Triamcinolone acetonide injection (Kenalog) is also used in clinical practice in ocular inflammatory conditions, but not specifically labeled for periocular use. Because triamcinolone acetonide injection (Kenalog) contains benzyl alcohol, it cannot be used intravitreally. [5]
    * Methylprednisolone (Depot Medrol) is also used for periocular injections (but not intraocular/intravitreal injection). [3]
    * However, Triesence (triamcinolone acetonide injection) is the only commercially available injectable steroid for intravitreal use. Other intravitreal steroid formulations include implants.
    * Xipere (triamcinolone acetonide suprachoroidal) is injected suprachoroidally, a newer route of administration without significant clinical experience. [6]

Clinical Efficacy

- The efficacy of Xipere (triamcinolone acetonide suprachoroidal) was assessed in a 6-month, randomized, multicenter, double-masked, sham-controlled trial in patients with macular edema (ME) associated with non-infectious uveitis (PEACHTREE; n=160). [7,8]
    * The trial evaluated patients with non-infectious uveitis: anterior-, intermediate-, posterior-, or pan-uveitis.
    * Use of systemic corticosteroids (prednisone ≤ 20 mg/day or equivalent) and/or stable doses of systemic immunomodulatory therapies were allowed during the trial. Concomitant use with other corticosteroids, including topical ocular, intraocular and periocular injection, and intraocular implants, was not allowed at randomization; however, rescue therapy was allowed beginning at week 4.
    * Patients were randomized to Xipere (triamcinolone acetonide suprachoroidal) 4 mg or sham-control, administered at baseline and week 12.
    * The primary efficacy endpoint was the proportion of patients with best corrected visual acuity (BCVA) improved ≥15 letters from baseline after 24 weeks.
    * Xipere (triamcinolone acetonide suprachoroidal) was superior to placebo (sham) for improvement of vision (BCVA) at 24 weeks (47% vs. 16%, respectively). However, several flaws limit utility of the data for use of Xipere (triamcinolone acetonide suprachoroidal) in clinical practice:
        ▪ Patients in the trial were allowed to use other baseline anti-inflammatories, such the true effect of Xipere (triamcinolone acetonide suprachoroidal) is unclear.
        ▪ Given the lack of active comparator, the benefit of Xipere (triamcinolone acetonide suprachoroidal) relative to standard of care oral, topical, or intravitreal corticosteroids and systemic immunomodulatory therapies remains unknown.
        ▪ The trial was of short duration for a chronic condition; durability of response is currently unknown. In addition, any benefit from suprachoroidal steroid administration, such as reduction in cataracts or exacerbation of glaucoma, remains unproven with the available evidence.
- Xipere (triamcinolone acetonide suprachoroidal) has not been compared to any of the other available steroid formulations. Systematic reviews consider the use of existing triamcinolone acetonide formulations (such as Triesence) safe and effective for periocular and intravitreal use. [9,10]
- Xipere (triamcinolone acetonide suprachoroidal) has not been studied in a well-designed RCT in any other causes of ME, such as diabetic ME (DME), retinal vein occlusion (central or branch; CRVO, BRVO), or age-related (wet) macular degeneration (wAMD). The approach to treatment of these non-uveitis causes of macular edema do not use topical and oral steroids as standard treatments.

Investigational Uses

- There are no published clinical trials evaluating the safety or efficacy of Xipere (triamcinolone acetonide suprachoroidal) in any other route of administration aside from suprachoroidally.

Safety [1, 8, 9]

- There is no evidence that Xipere (triamcinolone acetonide suprachoroidal) is safer than other corticosteroid options, including periocular/intravitreal triamcinolone acetonide (Triesence).
- Elevations in intraocular pressure (IOP), exacerbation of glaucoma, and cataract development or progression are known adverse events (AEs) with use of intravitreal corticosteroids, resulting from corticosteroid exposure to the anterior segment and the lens. However, the available trial data for Xipere (triamcinolone acetonide suprachoroidal) is insufficient to conclude lower rates of these intraocular complications with the use of suprachoroidal administration.
- At this time, the overall, AE rates with Xipere (triamcinolone acetonide suprachoroidal) appear generally comparable to periocular/intraocular (intravitreal) administered corticosteroids, such as triamcinolone acetonide periocular/intravitreal (Triesence). However, given the absence of a direct comparative trial, any conclusion of superior safety of triamcinolone acetonide suprachoroidal (Xipere) is not possible.

Appendix 1: Duration of action of long-acting ophthalmic corticosteroids

Formulation	Duration of Action
Iluvien (fluocinonide implant)	36 months
Ozurdex (dexamethasone implant)	6 months
Retisert (fluocinonide implant)	36 months
Yutiq (fluocinonide implant)	30 months

Codes	Number	Description
HCPCS	J3299	Injection, triamcinolone acetonide (Xipere), 1 mg

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Revision History

Revision Date	Revision Summary
3/21/2024	No criteria changes with this annual review.
3/16/2023	No criteria changes with this annual update.
3/18/2022	Effective 4/15/2022: New policy. Limits coverage to when lower cost forms of corticosteroids were ineffective, including topical ophthalmics, oral, and triamcinolone acetonide injection (periocular or intravitreal).

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Medication Policy Manual **Policy No:** dru705

Topic: Medications for T-Cell Lymphoma **Date of Origin:** June 1, 2022

- Beleodaq, belinostat
- Lymphir, denileukin diftitox-cxdl
- pralatrexate (generic, Folotyn)
- romidepsin (generic, Istodax)

Committee Approval Date: March 6, 2025 **Next Review Date:** 2026

Effective Date: May 1, 2025

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Medications in this policy are cancer medications used in the treatment of certain types of T-cell lymphomas. They are administered via intravenous infusion.

Policy/Criteria

Most contracts require pre-authorization approval of Medications for T-cell lymphoma (as listed in Table 1) prior to coverage.

I. Continuation of therapy (COT): Medications for T-cell lymphoma may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note: *Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Medications for T-cell lymphoma (as listed in *Table 1*) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that the applicable diagnosis-based criteria and step therapy below are met:

Table 1:

Diagnosis	Coverable Medication(s)	ALL of the following diagnostic criteria are met:
Peripheral T-cell Lymphoma (PTCL)	- Beleodaq (belinostat) - pralatrexate (generic, Folotyn) - romidepsin (generic, Istodax)	**1.** A confirmed diagnosis of PTCL. **2.** At least two prior systemic therapy regimens for PTCL were ineffective or not tolerated (see *Appendix 1*). **3.** Will be used as monotherapy.
Cutaneous T-cell Lymphoma (CTCL)	- Lymphir (denileukin diftitox-cxdl) - romidepsin (generic, Istodax)	**1.** A confirmed diagnosis of CTCL [e.g., Mycosis Fungoides (MF) and Sézary Syndrome]. **2.** At least two prior systemic therapy regimens have been ineffective or not tolerated (see *Appendix 2*). **3.** Will be used as monotherapy.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Medications for T-cell lymphoma (as listed in *Table 1*) coverable only under the medical benefit (as provider-administered medications).

B. When pre-authorization is approved, Medications for T-cell lymphoma will be authorized up to the limits in *Table 2* below, until disease progression.

Table 2:

Medication	Quantity Limit
Beleodaq (belinostat)	Up to five infusions every three weeks.
Lymphir (denileukin diftitox)	Up to five infusions every three weeks.
pralatrexate (generic, Folotyn)	Up to four infusions every four weeks.
romidepsin (generic, Istodax)	Up to three infusions every four weeks.

C. Authorization **may** be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

IV. Investigational Uses:

A. Unless otherwise specified in the coverage criteria above, medications included in this policy are considered investigational when used for all other conditions, due to lack of published data, lack of high-quality data, or lack of positive data.

B. Sequential use of HDAC inhibitors [Beleodaq (belinostat) or romidepsin (generic, Istodax)] after disease progression (and/or disease non-response) on prior HDAC inhibitor therapy.

C. HDAC inhibitors [Beleodaq (belinostat), romidepsin (generic, Istodax), or pralatrexate (generic, Folotyn)]: when used in combination with other chemotherapy medications.

Position Statement

Summary

- "Medications for T-cell lymphoma" are intravenously (IV) administered medications approved for the treatment of several specific T-cell cancers.
- The intent of this policy is to cover medications for T-cell lymphoma in the clinical settings where they have been shown to be safe and effective, as detailed in the coverage criteria, with consideration for other available treatment options.
    * Where there is lack of proven additional benefit and/or lack of demonstrated health outcomes (such as overall survival or improved quality of life) relative to alternative therapies, use of "Medications for T-cell lymphoma" is not coverable ("not medically necessary" or "investigational").
- "Medications for T-cell lymphoma" include the following:
    * Pralatrexate (generic, Folotyn), a methotrexate analog, is used in the treatment of peripheral T-cell lymphoma (PTCL), including the various subtypes of PTCL (*see Appendix 1*).
    * Beleodaq (belinostat), a histone deacetylase (HDAC) inhibitor, is also used for the treatment of relapsed or refractory PTCL.
    * Romidepsin (generic, Istodax), another HDAC inhibitor, is among several systemic medications (see *Appendix 2*) that may be used to treat cutaneous T-cell lymphoma (CTCL) [e.g., Mycosis Fungoides (MF), Sézary Syndrome (SS)]. It was previously FDA approved for use in relapsed/refractory PTCL after one prior therapy; however, because a confirmatory trial in first-line treatment failed to meet the primary endpoint, the FDA indication for PTCL was withdrawn. However, given that the evidence for romidepsin (generic, Istodax) in the salvage setting has not changed, the policy stance for coverage of romidepsin (generic, Istodax) for PTCL after two prior therapies remains unchanged.
    * Lymphir (denileukin diftitox-cxdl), an interleukin-2 (IL2)-receptor-directed cytotoxin, is used in the treatment of relapsed or refractory CTCL (e.g., MF or SS). *[Note: Lymphir is a new purified formulation of denileukin diftitox. It replaces Ontak, an older formulation, which was withdrawn from the market in 2014 due to production purity issues]*
- The effectiveness of "Medications for T-cell lymphoma" is based on low-quality, uncontrolled studies that evaluated surrogate endpoints (tumor response and duration of response). The effect of these therapies on overall survival has not been evaluated. Additional studies are necessary to describe and verify a clinical benefit, as these surrogate endpoints have not been shown to correlate with clinically meaningful outcomes.
- "Medications for T-cell lymphoma" were studied in patients who had prior systemic therapy for their PTCL or CTCL. However, prior treatment with other HDAC inhibitors was not allowed in the trials of HDAC inhibitors Beleodaq (belinostat) and romidepsin (generic, Istodax).
- None of the "Medications for T-cell lymphoma" have been compared to any other therapy options. Therefore, no one treatment option is known to be superior to another.

- National Comprehensive Cancer Network (NCCN) guidelines list many options for the treatment of PTCL and CTCL, including the medications in this policy.
- "Medications for T-cell lymphoma" are administered intravenously (IV) and given until disease progression or unacceptable toxicity.
- "Medications for T-cell lymphoma" are being studied in a variety of other cancers; however, there is insufficient evidence supporting safety and efficacy in these other conditions at this time.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy

PERIPHERAL T-CELL LYMPHOMA (PTCL)

- *Beleodaq (belinostat):* The efficacy of Beleodaq (belinostat) is based on a single, uncontrolled study in patients with relapsed or refractory PTCL (n=129), with surrogate endpoints, tumor response and duration of response, not tied to clinically relevant outcomes. [1]
    - Patients in the trial had a median of two prior therapies for PTCL (range of 1 to 8) and a life expectancy of at least 3 months. Prior therapy with a histone deacetylase (HDAC) inhibitor [e.g., Istodax (romidepsin)] was not allowed.
    - The overall response rate among the 120 evaluable patients was 25.8%, with a median duration of response of 8.4 months.
- *Pralatrexate (generic, Folotyn):* The efficacy of pralatrexate (generic, Folotyn) is based on a single, uncontrolled study in patients with relapsed or refractory PTCL (n=111) that used response criteria as its primary outcome. [2]
    - The median number of prior systemic therapies was 3 (range 1 to 12).

    * Overall response rate was defined as the sum of the complete response rate, unconfirmed complete response rate, and partial response rate.
- Tumor response rates and duration of response are surrogate endpoints, not proven to correlate with clinically relevant outcomes for patients with PTCL.
- There is currently no evidence that Beleodaq (belinostat) or pralatrexate (generic, Folotyn) improve clinical outcomes such as progression-free survival or overall survival in PTCL.
- It is not known how Beleodaq (belinostat) or pralatrexate (generic, Folotyn) compare with other PTCL therapies; neither have not been directly compared with placebo or any other therapy.
- *Romidepsin (generic, Istodax):* was FDA approved based on 25% improvement in overall response rate in an uncontrolled trial in patients with previously treated PTCL (n=130) who had failed at least one prior therapy. [3] A second trial in a mixed group of patients with PTCL or CTCL was used as supportive information. [4] Most recently, the follow-up phase 3 confirmatory trial failed to meet the primary endpoint of progression-free survival (PFS) as a first-line therapy for PTCL. [5] In mid-2021, the FDA indication for Istodax (romidepsin) was withdrawn for PTCL after ten years on the market. However, the available evidence for use of Istodax (romidepsin) in relapsed/refractory PTCL remains unchanged.
- The NCCN T-cell lymphoma guideline lists several potential options for the subsequent treatment of PTCL (see *Appendix 1*), including Beleodaq (belinostat), pralatrexate (generic, Folotyn), and romidepsin (generic, Istodax), meaning the quality of evidence is low, but there was consensus among oncologists on the panel for inclusion on the guideline. [6]

CUTANEOUS T-CELL LYMPHOMA (CTCL)

- *Istodax (romidepsin):* The effectiveness of romidepsin (generic, Istodax) has been evaluated in 167 subjects with cutaneous T-cell lymphoma (CTCL) in two, uncontrolled clinical trials with poor quality evidence. [7 8]
    * There was no comparator in either of the studies.
    * The studies evaluated a subgroup of subjects with CTCL for overall response (partial response plus complete response) to therapy.
    * Approximately 34% of subjects had either a partial response (28%) or a complete response (6%).
    * All subjects evaluated in the studies had been on one or more prior systemic therapies.
    * There is currently no evidence that romidepsin (generic, Istodax) improves clinical outcomes (e.g., overall survival, quality of life) in patients with CTCL.
- *Lymphir (denileukin diftitox):* The efficacy of Lymphir (denileukin diftitox) in relapsed or refractory CTCL is based on a single-arm, open-label, low-quality study [Study 302] in 69 subjects with stage I to III mycoses fungoides (MF) or Sézary syndrome (SS). [9 10]
    * The proportion of patients with MF and SS was not identified.

    * The median number of prior therapies received was four (includes both systemic and skin-directed therapies).
    * Prior therapies included: Systemic retinoids (49%), methotrexate/pralatrexate (49%), a histone deacetylase inhibitor (35%), Adcetris (brentuximab vedotin) (26%), and Poteligeo (mogamulizumab) (12%).
    * The objective response rate (ORR) was 36% with 6 (9%) complete responses.
- The NCCN T-cell Lymphomas and Primary Cutaneous Lymphomas guideline lists: [11]
    * Romidepsin (generic, Istodax) among several recommended systemic treatment options for the treatment of CTCL [refer to *Appendix 2*].
    * Lymphir (denileukin diftitox) among its recommendations for MF; however, it is not listed a recommendation for SS.

OTHER CANCERS:

- To date, the activity of Beleodaq (belinostat) in the following cancers has not been promising: [12-17] mesothelioma, carcinoma of unknown primary site (CUP), and myelodysplastic syndromes. There are several small, published, preliminary trials that studied Beleodaq (belinostat) in other types of cancer including thymic cancers, ovarian cancer, and hepatocellular carcinoma. Larger, comparative studies are needed to establish clinical benefit in these conditions. There is limited evidence for efficacy (i.e., response rates) in this setting. [18] Larger, well-controlled studies are needed to confirm preliminary findings.
- Pralatrexate (generic, Folotyn) is being studied in the treatment of several additional conditions including other types of non-Hodgkin's lymphomas, non-small cell lung cancer (NSCLC) and mesothelioma. There is also interest in using pralatrexate (generic, Folotyn) as a front-line therapy for patients with PTCL.
    * Results from most of the non-Hodgkin's lymphoma studies (other than PTCL) have not been reported in peer-reviewed literature. [10]
    * In a small, published trial Folotyn (pralatrexate) demonstrated some activity in patients with NSCLC based on objective response rates. [19] A second, published trial comparing pralatrexate (generic, Folotyn) and erlotinib used overall survival as a primary endpoint. No statistical difference was reported; however, the trial was not adequately powered to detect a difference between interventions, so results are not meaningful. [20] Larger, well-controlled studies are needed to establish the safety and efficacy of pralatrexate (generic, Folotyn) in NSCLC.
    * A single small trial failed to demonstrate any benefit from single-agent pralatrexate (generic, Folotyn) in patients with malignant pleural mesothelioma. [21]
    * When used as a front-line therapy for PTCL, the addition of pralatrexate (generic, Folotyn) to conventional chemotherapy (i.e., cyclophosphamide, doxorubicin, vincristine, prednisone), did not improve outcomes compared to historical data using chemotherapy alone. [22]

    - Small, preliminary studies evaluated tumor response in patients (N = 49) who were given carboplatin plus pralatrexate (generic, Folotyn) for recurrent, platinum-sensitive ovarian, fallopian tube, or primary peritoneal cancer. Controlled trials are needed to establish clinical benefit in this population. [23]
- Istodax (romidepsin) is being evaluated for use in several other conditions:
    - Preliminary studies failed to demonstrate a benefit in advanced colorectal cancer, metastatic renal cell carcinoma, prostate cancer, and lung cancer. [24-28]
    - A phase 2 study evaluated the combination of romidepsin (generic, Istodax) and gemcitabine in patients with relapsed or refractory PTCL. There was no additional benefit shown over the use of romidepsin (generic, Istodax) alone. [29]
    - In small number of patients with relapsed multiple myeloma, poor response rates were achieved. [30]
    - No results are available for studies in several other conditions including squamous cell cancer of the head and neck (SCCHN), breast cancer, solid tumors, and acute myelogenous leukemia. [10]
- Lymphir has not been studied in other T-cell lymphomas to date. *[Note: Lymphir is a new purified formulation of denileukin diftitox. It replaces Ontak, an older formulation, which was withdrawn from the market in 2014 due to production purity issues]*

Dosing [31]

- Beleodaq (belinostat) is given intravenously (IV) on days 1 through 5 of a 21-day cycle.
- Pralatrexate (generic, Folotyn) is given IV push once weekly for 6 weeks in 7-week cycles.
- Romidepsin (generic Istodax) is given IV on days 1, 8, and 15 of every 28-day cycle.
- Lymphir (denileukin diftitox) is given IV on days 1 through 5 of each 21-day cycle.
- Administration of each of these therapies is continued until disease progression or unacceptable toxicity.

Appendix 1: Systemic Treatment Options for PTCL [11] [a,b,c]	
First-line Therapy	
• Adcetris (brentuximab vedotin) + CHP (cyclophosphamide, doxorubicin, prednisone) for CD30+ histologies [a] • CHOEP (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone) • CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) • CHOP followed by IVE (ifosfamide, etoposide, epirubicin) alternating with methotrexate • Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)	
Second-line Therapy	
Transplant candidates	*Non-transplant candidates*
• *Preferred single agents:* o Adcetris (brentuximab vedotin) for CD30+ PTCL o Beleodaq (belinostat) o Pralatrexate (generic, Folotyn) o Romidepsin (generic, Istodax) o Duvelisib (Copiktra) • *Preferred combination regimens:* o DHA (dexamethasone, cisplatin, cytarabine) o ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) o GDP (gemcitabine, dexamethasone, cisplatin) o GemOx (gemcitabine, oxaliplatin) o ICE (ifosfamide, carboplatin, etoposide) • *Other recommended single agents/regimens:* o Bendamustine o Gemcitabine o GVD [gemcitabine, vinorelbine, liposomal doxorubicin (generic, Doxil)] o lenalidomide (generic, Revlimid)	• *Preferred single agents/regimens:* o Adcetris (brentuximab vedotin) for CD30+ PTCL o Beleodaq (belinostat) o Pralatrexate (generic, Folotyn) o Romidepsin (generic, Istodax) o Duvelisib (Copiktra) • *Other recommended single agents:* o Alemtuzumab o Bendamustine o Campath (alemtuzumab) o Cyclophosphamide and/or etoposide (IV or PO) o Gemcitabine o Radiation therapy o lenalidomide (generic, Revlimid)
[a] PTCL subtypes included: PTCL not otherwise specified (NOS), angioimmunoblastic T-cell lymphoma (AITL), anaplastic large cell lymphoma (ALCL), enteropathy-associated T-cell lymphoma (EATL), monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL) [b] All therapies listed above are NCCN category 2A recommendations (lower quality evidence but uniform consensus among panel) unless otherwise indicated. [c] AITL and ALCL have slight variations in the regimens used in the second line and subsequent therapy setting	

Appendix 2: Systemic Treatment Options for CTCL (i.e. Mycosis Fungoides (MF)/Sezary Syndrome) [a] [6]	
Actimmune (interferon gamma)	Leukeran (chlorambucil)
Adcetris (brentuximab vedotin)	Lymphir (denileukin diftitox-cxdl)
Campath (alemtuzumab)	methotrexate
liposomal doxorubicin (generic, Doxil)	Poteligeo (mogamulizumab)
pralatrexate (generic, Folotyn)	acitretin (generic, Soriatane)
gemcitabine	bexarotene (generic, Targretin)
Intron A (interferon alfa)	temozolomide (CNS involvement)
isotretinoin	Vesanoid (all-trans retinoic acid)
romidepsin (generic, Istodax)	Zolinza (vorinostat)
Keytruda (pembrolizumab) [category 2B]	
[a] All therapies listed above are NCCN category 2A recommendations (lower quality evidence but uniform consensus among panel), unless otherwise noted.	

Cross References
Adcetris, brentuximab vedotin, Medication Policy Manual, Policy No. dru264

Codes	**Number**	**Description**
HCPCS	J9032	Injection, belinostat (Beleodaq), 10 mg
HCPCS	J9318	Injection, romidepsin (Istodax), non-lyophilized, 0.1 mg
HCPCS	J9319	Injection, romidepsin (Istodax), lyophilized, 0.1 mg
HCPCS	J9307	Injection, pralatrexate (Folotyn), 1 mg

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Revision History

Revision Date	Revision Summary
3/6/2025	No changes to coverage criteria with this annual review.
12/12/2024	Added coverage for Lymphir, a new and purer formulation of denileukin diftitox, for CTCL after two prior systemic therapies. All other uses are considered investigational.
6/20/2024	No criteria changes with this annual review.
12/7/2023	No criteria changes with this annual review.
3/16/2023	No changes to coverage criteria with this annual update.
12/9/2022	• Updated standard language in policy. • No changes to coverage criteria with this annual update.
3/18/2022	New combination policy, effective 6/1/2022: Combined the following medication policies: dru362 Beleodaq, belinostat, dru198 Istodax, romidepsin, and dru197 Folotyn, pralatrexate. No change to the intent of pre-existing criteria with the following exceptions: - Removal of Istodax (romidepsin) step therapy for coverage of medications for PTCL, as the FDA indication for PTCL was withdrawn by the manufacturer based on a failed trial of Istodax (romidepsin) in the front-line setting. - Clarification of intent of monotherapy and sequential HDAC therapy.

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Medication Policy Manual | **Policy No:** dru711

Topic: Skysona, elivaldogene autotemcel | **Date of Origin:** July 15, 2023

Committee Approval Date: March 21, 2024 | **Next Review Date:** 2025

Effective Date: June 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Skysona (elivaldogene autotemcel) is an intravenous (IV) medication that is used to treat a rare, genetic condition (cerebral adrenoleukodystrophy).

Policy/Criteria

Most contracts require pre-authorization approval of Skysona (elivaldogene autotemcel) prior to coverage.

I. Continuation of therapy (COT): Skysona (elivaldogene autotemcel) may be considered medically necessary for COT when full policy criteria below are met, including quantity limit.

Please note: *Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Skysona (elivaldogene autotemcel) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A and B below are met.

A. The patient is a suitable candidate for Skysona (elivaldogene autotemcel) and meets all of the following criteria (1 and 2) below:

1. No prior use of gene therapy

AND

2. Patient is fit for therapy, as defined by meeting all the criteria below:

a. The patient is clinically stable and eligible for an Allo-HSCT but does NOT have an available HLA-matched donor (provider attestation).

AND

b. The patient has adequate and stable kidney, liver, and cardiac function (provider attestation).

AND

c. The patient has no active systemic infections (including, but not limited to HCV, HBV, and HIV infection) (provider attestation).

PLEASE NOTE: Suitability for therapy must be documented in recent clinical documentation (such as in chart notes, laboratory reports), which MUST include evaluation for HSCT [bone marrow transplant BMT)].

AND

B. A diagnosis of **early, active cerebral adrenoleukodystrophy** (CALD) when there is clinical documentation that all criteria 1 through 7 below are met:

1. The diagnosis is genetically confirmed (adenosine triphosphate binding cassette, sub family D member 1 [ABCD1] gene).

AND

2. No prior allogeneic hematopoietic stem cell transplantation (allo-HSCT).

AND

3. Neurologic function score (NFS) less than or equal to 1.

AND

4. Gadolinium enhancement (GdE+) on brain magnetic resonance imaging (MRI).

AND

5. Loes score between 0.5 and 9.

AND

6. Elevated very long chain fatty acids (VLCFA) values per reference range of the laboratory performing the test.

AND

7. Patient does not have isolated pyramidal tract disease.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Skysona (elivaldogene autotemcel) coverable under the medical benefit (as a provider administered medication).

B. When pre-authorization is approved, Skysona (elivaldogene autotemcel) will be authorized in quantities of one treatment course per lifetime.

C. Additional infusions of Skysona (elivaldogene autotemcel) will not be authorized.

IV. Skysona (elivaldogene autotemcel) is considered investigational when used for all other conditions.

Position Statement

Summary

- Skysona (elivaldogene autotemcel) is an ex-vivo gene therapy. It adds functional copies of the adenosine triphosphate binding cassette, subfamily D, member 1 (ABCD1) gene into hematopoietic stem cells using a replication-deficient, self-inactivating lentiviral vector (LVV).
- Skysona (elivaldogene autotemcel) is a one-time IV infusion. However, it is a very complex, high-cost therapy and requires several phases of administration, extended hospitalization, and extensive supportive care, similar to a hematopoietic stem cell transplantation (HSCT).
- The intent of this policy is to allow for coverage of Skysona (elivaldogene autotemcel) for the indication and dose for which it has been shown to be safe and effective in clinical trials. This includes genetically confirmed early, active CALD in patients that are clinically stable and eligible for an allo-HSCT, but do not have an available HLA-matched donor (related or unrelated) and the patient does not have isolated pyramidal tract disease.
- Current evidence for Skysona (elivaldogene autotemcel) is limited to small, single-arm, non-randomized trials that evaluated the proportion of patients who were alive and had none of the predefined Major Functional Disabilities (MFD) at Month 24. MFD-free

survival was achieved in the majority of genetically confirmed early, active CALD patients; however, the generalizability of the results and the long-term impact of Skysona (elivaldogene autotemcel) on other clinically relevant outcomes, such as overall survival (OS), is unknown at this time.

- For those with early, active disease, the standard of care is an allo-HSCT. It is the only known treatment that has demonstrated the ability to stabilize or slow the progression of disease. However, many patients with early, active CALD do not have a HLA-matched donor for HSCT. For these specific populations, the potential benefit of Skysona (elivaldogene autotemcel) may outweigh the risks.
- Significant safety issues are directly associated with the use of Skysona (elivaldogene autotemcel). In particular, the risk of hematologic malignancies is especially notable, given the high frequency of LVV integrations into proto-oncogenes.
- At this time, there is not enough data available to determine that the benefit of Skysona (elivaldogene autotemcel) use would outweigh the risks or provide any meaningful benefit long-term in those transplant-eligible patients with an available HLA-matched donor (both related and unrelated). However, in patients without an HLA-matched donor, the benefits may outweigh the risks due to the unmet need in this population.

Clinical Efficacy

- Skysona (elivaldogene autotemcel) was granted accelerated approval by the FDA based on post-hoc exploratory endpoints from a small subset of patients enrolled in two open-label trials. Patients in both trials had early, active CALD, were between 4 to 17 years of age, a Neurologic Function Score (NFS) ≤ 1, and were without an HLA-matched sibling donor.
- The first trial, ALD-102, is an ongoing multicenter, single arm, phase 2/3 trial in which all subjects (n=32) received a single infusion of Skysona (elivaldogene autotemcel) at a dose of ≥5 x 10^6 $CD34^+$ cells/kg after completion of conditioning regimens.
    * The primary endpoint for this trial was the proportion of patients who were alive and had none of the predefined Major Functional Disabilities (MFD) at Month 24, also known as MFD-free survival.
        - The defined MFDs are clinically relevant to the CALD population, and included the following: loss of communication, cortical blindness, tube feeding, total incontinence, wheelchair dependence, and complete loss of voluntary movement.
- The second trial, ALD-104, is an ongoing multicenter, single arm, phase 3 trial (n=35) and was similar in design to ALD-102. At the time of the data cut, the median follow-up was 6.3 months. As such, the primary efficacy endpoint could not be assessed at this time.
- Given the single arm nature of ALD-102 and ALD-104, and the heterogenous nature of CALD, the FDA utilized external control data derived from a retrospective natural history study, ALD-101, which consisted of untreated CALD patients, as a basis for evaluating the efficacy of Skysona (elivaldogene autotemcel).
    * Despite a high MFD-free response rate, the FDA could not rely on the primary endpoint from the ALD-102 trial to support approval due to the following reasons:

    - Lack of comparability between Skysona (elivaldogene autotemcel) treated subjects and the natural history populations.
    - Insufficient length of study to ensure that the clinical results (lack of MFDs) were not simply due to early disease identification.
    - Overestimation of the number of failure events in the allo-HSCT-treated early, active disease subpopulation.
- Therefore, the basis for approval was primarily due to a post-hoc time to event analysis (time to progression to MFD or death from first disease symptom (NFS ≥ 1)), in a small symptomatic subset of Skysona (elivaldogene autotemcel) treated subjects which demonstrated a slowed progression of neurologic dysfunction compared to the expected natural history.
    * MFD-free survival KM estimates at the 24-month time point were 43%, 69%, and 72% for the untreated (n=7), allo-HSCT treated (n=16) and elivaldogene autotemcel (n=11) symptomatic subpopulations, respectively.
- Patients with isolated pyramidal tract disease often have slower progressing disease that does not appear until adulthood. In ALD-102, participants with isolated pyramidal tract disease had a worse response to Skysona (elivaldogene autotemcel) than other cohorts. As a result, the following was included in the FDA package insert:
    * Given the risk of hematologic malignancy with elivaldogene autotemcel , and unclear long-term durability of Skysona (elivaldogene autotemcel), and human adrenoleukodystrophy protein (ALDP) expression, careful consideration should be given to the timing of treatment for each boy and treatment of boys with isolated pyramidal tract disease as clinical manifestations do not usually occur until adulthood.

Clinical Guidelines/Standard of Care Treatment

- The treatment of patients with CALD requires a multidisciplinary approach due to the number of complications associated with the disease.
- Currently, for those with early, active disease (Loes score 0.5-9, Gadolinium enhancement on MRI, and NFS ≤1), allo-HSCT is the only known treatment that has demonstrated the ability to stabilize or slow the progression of disease. However, use of allo-HSCT is limited by availability of HLA-matched donors for the stem cell donation.
    * Although effective, allo-HSCT is associated with known risks, including graft rejection, graft versus host disease, and infection. This risk is increased in those without an HLA-matched donor.
- For those with more advanced disease (Loes score >9), allo-HSCT is no longer recommended, as it may increase the rapidity of disease progression. Treatment in this population is predominantly supportive in nature.

Investigational Uses

- Skysona (elivaldogene autotemcel) is considered investigational when used for all other conditions.

Safety

- Skysona (elivaldogene autotemcel) is associated with a serious risk of hematologic malignancy, which is noted in the FDA label.
    * Insertional oncogenesis is a serious adverse event directly associated with LVV therapies, including Skysona (elivaldogene autotemcel).
    * There were 3 patients treated with elivaldogene autotemcel that developed a hematologic malignancy (myelodysplastic syndrome) as a direct result of the treatment. Additional hematologic malignancies are expected to arise.
- The most common side effects (>20% incidence) experienced during the ALD-102 trial were consistent with expected AEs from use of a conditioning regimen.
- Additional long-term follow-up is necessary to further define the safety profile of elivaldogene autotemcel in CALD patients. This includes the long-term risk of oncogenesis.

Codes	Number	Description
ICD-10	E71.520	Childhood cerebral X-linked adrenoleukodystrophy

References

1. Elenburg S, Crisafi L. Center for Drug Evaluation and Research; U.S. Food and Drug Administration: Elivaldogene Autotemcel Clinical Review Memorandum. Available from: https://www.fda.gov/vaccines-blood-biologics/skysona
2. Skysona® (elivaldogene autotemcel) [package insert]. Somerville, MA: Bluebird Bio; September 2022.

Revision History

Revision Date	Revision Summary
3/21/2024	No criteria changes with this annual review.
6/15/2023	New policy. Effective 7/15/2023. • Limits use to genetically confirmed early, active CALD in patients that are clinically stable and eligible for an Allo-HSCT, but do not have an available HLA-matched donor (related or unrelated) and the patient does not have isolated pyramidal tract disease.

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Medication Policy Manual

Policy No: dru716

Topic: Enjaymo, sutimlimab-jome

Date of Origin: July 15, 2022

Committee Approval: June 20, 2024

Next Review Date: 2025

Effective Date: July 15, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Enjaymo (sutimlimab-jome) is an intravenously administered medication used to treat a rare condition, cold agglutinin disease (CAD).

Policy/Criteria

Most contracts require pre-authorization approval of Enjaymo (sutimlimab-jome) prior to coverage.

I. Continuation of therapy (COT): Enjaymo (sutimlimab-jome) may be considered medically necessary for COT when full policy criteria below are met, including quantity limit.

Please note: *Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Enjaymo (sutimlimab-jome) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A through G below are met.

A. Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, Site of Care Review, dru408].

AND

B. A diagnosis of **cold agglutinin disease** (CAD), established by or in consultation with a hematologist.

AND

C. Presence of symptomatic anemia related to CAD.

AND

D. At least one documented red blood cell transfusion (RBCT) within the past 6 months.

AND

E. Rituximab-containing regimen used for the treatment of CAD has been ineffective, not tolerated, or use is contraindicated.

AND

F. Hemoglobin (Hgb) level ≤10.0 g/dL

AND

G. Total bilirubin level is above the normal reference range.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Enjaymo (sutimlimab-jome) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Enjaymo (sutimlimab-jome) will be authorized be authorized up to the following weight-based dosing:

1. For patients weighing less than 75 kg: 6,500 mg IV weekly for two weeks, then 6,500 mg IV every two weeks thereafter.

2. For patients weighing 75 kg or more: 7,500 mg IV weekly for two weeks, then 7,500 mg IV every two weeks thereafter.

C. Initial authorization up to 6 months. Reauthorization **shall** be reviewed every 12 months. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease symptom improvement or positive hematologic response (Hgb level increase or reduction in RBC transfusions).

IV. Enjaymo (sutimlimab-jome) is considered not medically necessary when used for CAD without a recent red blood cell transfusion (RBCT) (within the past 6 months).

V. Enjaymo (sutimlimab-jome) is considered investigational when used for all other conditions, including, but not limited to cold agglutinin syndrome (CAS).

Position Statement

Summary

- Enjaymo (sutimlimab-jome) is new complement inhibitor that may result in a decrease in hemolysis and need for RBC transfusions in patients with symptomatic cold agglutinin disease (CAD). Unlike B-cell targeted therapies (e.g., rituximab), Enjaymo (sutimlimab-jome) does not target the underlying cause of cold agglutinin disease and it does not improve the cold-induced ischemic symptoms of CAD.
- The intent of the policy is to allow coverage of Enjaymo (sutimlimab-jome) for patients with symptomatic CAD with a recent history of red blood cells (RBC) transfusions, after failure of rituximab-containing regimens, up to the dose shown to be safe and effective in clinical trials.
- CAD is a type of autoimmune hemolytic anemia (AIHA), which is triggered by cold temperatures.
- CAD is a heterogenous disease, with a range in severity and symptoms. Some CAD patients are asymptomatic with no treatment required, while others present with severe anemia and other cold-induced symptoms. Patients with symptomatic disease and a dependence on RBC transfusions may see benefit with Enjaymo (sutimlimab-jome), based on a reduction in hemolysis markers. However, Enjaymo (sutimlimab-jome) does not affect production of cold agglutinins or reduce resulting cold-ischemic symptoms of CAD.
- In symptomatic patients, CAD results in both hemolytic anemia (caused by complement pathway activation) and cold-induced ischemic symptoms (due to RBC agglutination).
- In patients with a history of recent transfusion, Enjaymo (sutimlimab-jome) use resulted in a clinical response in 54.2% of CAD patients.
- Enjaymo (sutimlimab-jome) was initially studied in symptomatic CAD patients with a history of RBC transfusions in the past 6 months and clinical laboratory markers of hemolytic anemia (Hgb ≤10.0 g/dL, total bilirubin ≥ ULN etc.).
- Subsequently, Enjaymo (sutimlimab-jome) was studied in asymptomatic CAD patients (withOUT a history of recent RBC transfusions). However, the use of Enjaymo (sutimlimab-jome) for CAD without a transfusion requirement is considered not

medically necessary, given the lack of clinically meaningful endpoints demonstrated during the trial.

- Rituximab-based regimens are considered first-line therapy, as they address all aspects of the disease pathophysiology (hemolysis and cold-induced ischemic symptoms), by reduction in the production of cold agglutinins by targeting the B-cells.
- In contrast, Enjaymo (sutimlimab-jome) only addresses hemolysis-related symptoms and must be taken indefinitely. Rituximab can be used for a short period of time, provides long-term benefits, and is a significantly less costly treatment option.
- Additional controlled trials are needed to assess the long-term safety and efficacy of Enjaymo (sutimlimab-jome), including improvement in quality of life (QOL), overall survival, impact on long-term complications, or benefit over existing treatment options.
- Enjaymo (sutimlimab-jome) may be covered in doses up to 6500 mg or 7,500 mg IV every 2 weeks, depending on weight. These are the doses at which it has been shown to be safe and effective.

Disease Background

- CAD accounts for ~15% of total AIHA cases and is the result of an indolent, clonal B-cell lymphoproliferative disorder that leads to an overproduction of cold agglutinins, which are IgM autoantibodies that target erythrocytes.
- When exposed to cold temperatures and internal temperatures drop below 37º C, cold agglutinins bind to the "I" antigen on RBCs. This triggers agglutination and activates the classic complement pathway when the IgM-antigen complex binds to the C1 complement complex.
- Secondary cold agglutinin syndrome (CAS) occurs when cold agglutinins arise due to an underlying condition. This syndrome is managed differently than CAD and Enjaymo (sutimlimab-jome) would not be used in this population.

Clinical Efficacy[1 2]

The safety and efficacy of sutimlimab in CAD in patients with recent transfusion was established based on one phase 3, multi-center, open-label, single-arm trial (CARDINAL) in patients with symptomatic CAD (n=24). Although sutimlimab improved hemolysis markers in half of treated patients with symptomatic CAD, sutimlimab does not reduce production of cold agglutinins, the cause of the hemolysis, nor reduce associated cold-ischemic symptoms of CAD.

- All patients had symptomatic CAD, laboratory findings consistent with hemolysis, and a history of RBC transfusions in the last six months.
    * Symptoms for enrollment included one of the following within the last 3 months: symptomatic anemia, acrocyanosis, Raynaud's syndrome, hemoglobinuria, disabling circulatory symptoms, or a major adverse vascular event.
    * Subjects were required to have a Hgb level ≤10 g/dL and bilirubin above the normal reference range.
- A majority of enrolled patients (62%; n=15) had been treated with rituximab in the past 5 years [monotherapy (n=12), rituximab/bendamustine (n=4), and rituximab/fludarabine (n=2)].

- The primary endpoint was treatment response at 26 weeks, based on a composite endpoint of hemolysis markers, defined as meeting all of the following:
    * No blood transfusions from Week 5 through Week 26.
    * No additional treatments started for CAD management.
    * Hgb level ≥12 g/dL (mean value from Weeks 23, 25, and 26) or Hgb increased ≥ 2 g/dL from baseline.
- Treatment response rate was 54.2%. Although sutimlimab reduced symptomatic CAD, based on hemolysis markers, sutimlimab does not reduce cold agglutinin production, the underlying cause of the hemolysis.
- Due to the short duration of the trial (26 eeks), it is unknown if sutimlimab will result in a clinically meaningful improvement in long-term QOL, overall survival, or a reduction in chronic complications.

Subsequently, sutimlimab was FDA approved in CAD in patients without a recent transfusion based a phase 3, double-blind, placebo-controlled, CADENZA trial. Although sutimlimab was studied compared to placebo in CAD patients without recent transfusion, evidence is insufficient that sutimlimab is safer or more effective than standard of care.

- The primary endpoint was treatment response at 26 weeks, based on a composite endpoint of hemolysis markers, defined as meeting all of the following:
    * No blood transfusions from Week 5 through Week 26.
    * No additional treatments started for CAD management.
    * Hgb level increased ≥ 1.5 g/dL from baseline.
- The response rate difference between sutimlimab and placebo was ~59% but appeared to be driven by increases in Hgb. There was as there was little to no difference in transfusions and use of prohibited medications for CAD.
- It is unknown how sutimlimab compares with standard of care for the management of CAD.

Standard of Care Treatment [3-6]

Management of CAD includes a variety of therapies and modalities to manage and prevent disease-related symptoms.

- Preventative: Cold temperature avoidance is effective at reducing cold-induced symptoms and hemolysis.
- Anemia management:
    * RBC transfusions are a valuable tool to manage symptomatic anemia.
    * Plasmapheresis can be used for acute critical hemolysis, to immediately remove cold agglutinins from the body.
- Reduction of cold agglutinins:
    * Short-term use of B-cell targeted therapies, such as rituximab-containing regimens) are considered first-line treatment to reduce the production of cold agglutinins by targeting the B-cells responsible for their production
    * Rituximab +/- bendamustine or fludarabine has the most evidence for efficacy and is most commonly used.

- Bind complement:
    * Anti-complement therapies target the classic complement pathway that leads to hemolysis. This can reduce the hemolysis markers and transfusion requirements and symptoms of anemia.
    * Of note, targeting this pathway does not impact the cells producing the cold agglutinins. Therefore, anti-complement therapies must be taken indefinitely and are not expected to improve cold-induced symptoms, such as acrocyanosis.

Safety [7]

- During clinical trials of sutimlimab, the most frequent adverse events (>10% incidence) were respiratory tract infection, viral infection, diarrhea, dyspepsia, cough, arthralgia, and peripheral edema.

Dosing [7]

- Sutimlimab is administered at a dose of 6,500 mg IV weekly for two weeks, then every two weeks thereafter for patients weighing less than 75 kg. The dose is increased to 7,500mg, at the same dosing frequency, for those weighing over 75kg.
- Efficacy and safety of dosing of sutimlimab in CAD patients in doses higher than mentioned above has not been established.

Cross References
Products with Therapeutically Equivalent Biosimilars/Reference Products, Medication Policy Manual, Policy No. dru620
Site of Care Review, Medication Policy Manual, Policy No. dru408

Codes	**Number**	**Description**
HCPCS	J1302	Injection, sutimlimab-jome (Enjaymo), 10 mg

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1. Roth A, Barcellini W, D'Sa S, et al. Sutimlimab in Cold Agglutinin Disease. *N Engl J Med*. 2021;384(14):1323-34. PMID: 33826820
2. Roth A, Berentsen S, Barcellini W, et al. Sutimlimab in patients with cold agglutinin disease: results of the randomized placebo-controlled phase 3 CADENZA trial. *Blood*. 2022;140(9):980-91. PMID: 35687757
3. Center for Drug Evaluation and Research; U.S. Food and Drug Administration: Clinical Review, sutimlimab (Enjaymo™). Secondary Center for Drug Evaluation and Research; U.S. Food and Drug Administration: Clinical Review, sutimlimab (Enjaymo™) [cited 5/3/2022]. 'Available from:' https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761164Orig1s000MedR.pdf.
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6. Rossi G, Gramegna D, Paoloni F, et al. Short course of bortezomib in anemic patients with relapsed cold agglutinin disease: a phase 2 prospective GIMEMA study. Blood. United States, 2018:547-50.
7. Enjaymo® (sutimlimab-jome) [package insert]. Waltham, MA: Bioverativ USA; 03/2023

Revision History

Revision Date	Revision Summary
6/20/2024	• Reauthorization updated to every 12 months. • Added site of care requirement. (effective 10/1/24)
9/14/2023	Added use of Enjaymo (sutimlimab-jome) in cold agglutinin disease (CAD) without a recent transfusion to "not medically necessary" uses.
6/17/2022	New policy (effective 9/1/2022). Limits coverage to patients with symptomatic cold agglutin disease (CAD) with recent need for RBC transfusions despite prior treatment with rituximab.

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Medication Policy Manual	**Policy No:** dru718
Topic: Opdualag, nivolumab-relatlimab-rmbw	**Date of Origin:** July 15, 2022
Committee Approval Date: September 19, 2024	**Next Review Date:** 2025
Effective Date: January 1, 2025	

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Opdualag (nivolumab-relatlimab-rmbw) is an intravenously administered immunotherapy approved for use in patients with advanced melanoma.

Policy/Criteria

Most contracts require pre-authorization approval of Opdualag (nivolumab-relatlimab-rmbw) prior to coverage.

I. Continuation of therapy (COT): Opdualag (nivolumab-relatlimab-rmbw) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan*

II. New starts (treatment-naïve patients): Opdualag (nivolumab-relatlimab-rmbw) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A, B, and C below are met:

A. A diagnosis of **melanoma**, unresectable or metastatic.

AND

B. No prior systemic therapy (including but not limited to prior use of PD-1 inhibitors or PD-L1 inhibitors) in the advanced disease setting (see *Appendix 1*).

AND

C. Opdualag (nivolumab-relatlimab-rmbw) will be used as monotherapy.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Opdualag (nivolumab-relatlimab-rmbw) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Opdualag (nivolumab-relatlimab-rmbw) may be approved for 24 weeks for up to one, 480 mg/160 mg infusion per month until disease progression.

C. Reauthorization: Authorization **shall** be reviewed at least every 24 weeks for documented benefit. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met. Specifically, documentation that the medication is providing clinical benefit, including disease stability or improvement, and lack of disease progression, based on an assessment of change in tumor burden. If there is documentation of potential disease progression, a shortened authorization (up to three months) may be approved to allow time for clarification of response to Opdualag (nivolumab-relatlimab-rmbw), including clinical re-evaluation of the patient and reimaging.

PLEASE NOTE: Additional doses of Opdualag (nivolumab-relatlimab-rmbw) will not be authorized without a documented recent assessment by the treating provider (such as oncologist) with objective evidence of response to therapy, such as by re-imaging and use of iRECIST criteria.

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IV. Opdualag (nivolumab-relatlimab-rmbw) is considered investigational when used for all other conditions, including but not limited to:

A. Subsequent therapy for previously-treated advanced melanoma: Use for disease progression/recurrence on/after use of systemic therapy in the advanced setting, including but not limited to, PD-1 inhibitors or PD-L1 inhibitors in the advanced setting (see *Appendix 1*).

B. Sequential use of PD-1 inhibitors or PD-L1 inhibitors (see *Appendix 1*)

Position Statement

Summary

- Opdualag (nivolumab-relatlimab-rmbw) is an intravenously administered immunotherapy. It is a combination of nivolumab, a programmed death receptor-1 (PD-1) blocking antibody and relatlimab, a lymphocyte activation gene-3 (LAG-3) blocking antibody. Blocking these pathways inhibits tumor growth and promotes tumor regression.
- The intent of this policy is to allow coverage of Opdualag (nivolumab-relatlimab-rmbw) in the clinical setting described in the coverage criteria above, where it has been evaluated for efficacy, up to the dose shown to be safe in clinical trials.
- The FDA approval of Opdualag (nivolumab-relatlimab-rmbw) was based on a fair quality randomized controlled trial [RELATIVITY-047] in patients with unresectable or metastatic melanoma who had no prior systemic therapy for their advanced disease. Opdualag (nivolumab-relatlimab-rmbw), when administered as monotherapy, was found to improve progression-free survival (PFS) relative to Opdivo (nivolumab).
    * PFS has not been proven to be an accurate predictor of OS or any other clinically relevant endpoint in advanced melanoma. Improved overall survival (OS) is the clinical outcome of interest in this disease setting. There is currently no information to determine if Opdualag (nivolumab-relatlimab-rmbw) improves OS relative to Opdivo (nivolumab) or any other melanoma therapy.
    * Seventy-five percent of patients enrolled in the pivotal trial had tumors with LAG-3 expression $\geq$ 1%. Both an early-stage trial and a subgroup analysis from the phase 2/3 pivotal trial suggest that LAG-3 expression $\geq$ 1% is associated with improved tumor response to Opdualag (nivolumab-relatlimab-rmbw) as compared with LAG-3 expression < 1%. Whether this has any application in the clinical setting is not yet known.
    * The use of Opdualag (nivolumab-relatlimab-rmbw) after disease progression/recurrence on/after chemotherapy and/or immunotherapy for advanced melanoma is not coverable at this time. A small percent of patients enrolled in the RELATIVITY-047 trial received prior immunotherapy in the non-advanced adjuvant setting for resectable melanoma. Patients with prior use of systemic therapy for advanced melanoma were excluded from the trial. Therefore, the use of Opdualag (nivolumab-relatlimab-rmbw) is coverable only when there is no prior systemic therapy in the advanced setting.
- The National Comprehensive Cancer Network (NCCN) cutaneous melanoma guideline lists Opdualag (nivolumab-relatlimab-rmbw) among its recommendations for front-line treatment of unresectable or metastatic melanoma when no BRAF V600 mutation is present.
- Opdualag (nivolumab-relatlimab-rmbw) may be covered in doses up to 480 mg/160 mg each month, the dose studied in the pivotal trial, until disease progression. This dose was established based on a weight of 40 kg or more. A dose for patients less than 40 kg has not been established. The safety and effectiveness of higher doses have not been established.

- The safety and effectiveness of Opdualag (nivolumab-relatlimab-rmbw) in conditions other than unresectable or metastatic melanoma have not been established.
- *Reauthorization Criteria*: When coverage criteria are met, Opdualag (nivolumab-relatlimab-rmbw) is authorized for six months (24 weeks) of therapy, after which time documentation must be provided to establish that the medication is effective. Specifically, there must be documentation of clinical benefit, including disease stability or improvement and there is a lack of disease progression, based on an assessment of change in tumor burden. Documentation of benefit must include an assessment of the most recent imaging ("restaging scans") and/or re-biopsy by the treating oncologist.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy

- The efficacy of Opdualag (nivolumab-relatlimab-rmbw) was studied in a fair quality randomized controlled trial [RELATIVITY-047] in patients with previously untreated, unresectable metastatic melanoma. The trial compared Opdualag (nivolumab-relatlimab-rmbw) with Opdivo (nivolumab) and evaluated progression-free survival (PFS) as the primary endpoint. [1]
    * Patients in the trial had no prior systemic therapy for their advanced disease. Approximately 8% of the population had prior adjuvant therapy which may have included immunotherapy or BRAF/MEK inhibitors; however, adjuvant therapy must have been completed at least 6 months prior to the current recurrence.
    * Approximately 90% of patients had metastatic disease and all had good performance status.

    * All patients were required to have a tumor tissue sample available for biomarker analysis. Randomization was stratified by PD-L1 expression, LAG-3 expression, BRAF status, and tumor stage.
    * Seventy-five percent of tumors had LAG-3 expression of at least 1%. In an earlier phase 1 study, a greater than 3-fold increase in tumor response to Opdualag (nivolumab-relatlimab-rmbw) was observed when LAG-3 expression was ≥ 1% versus < 1%.
- Median PFS was improved with Opdualag (nivolumab-relatlimab-rmbw) relative to Opdivo (nivolumab); however, there is no mature overall survival (OS) data available. OS is the clinical outcome of interest in this population. PFS has not been proven to be an accurate predictor of OS benefit. More information is needed before a better estimate of net health benefit can be made. [1]
- Additionally, similar to what was observed in an earlier phase 1 trial (Study CA224020), a subgroup analysis appears to show that tumors with a LAG-3 expression ≥ 1% show a better response to Opdualag (nivolumab-relatlimab-rmbw) than those with LAG-3 expression < 1%. [1] Whether this has any application in a clinical setting is yet to be determined.
- There is interest in the use of Opdualag (nivolumab-relatlimab-rmbw) as a subsequent therapy for metastatic melanoma, based on the Phase 1/2 RELATIVITY-020 trial, a single-arm, open-label trial in deeply pre-treated melanoma.[2] Given the lack of controls in the trial, overall low response rate compared to serious treatment-related adverse reaction rate, it is not known if patients are likely to benefit from sequential therapy. Additional trials are ongoing.
-

Guideline recommendations [3]

- The current National Comprehensive Cancer Network (NCCN) cutaneous melanoma guideline lists Opdualag (nivolumab-relatlimab-rmbw) among front-line options for unresectable or metastatic melanoma.
- Other therapies with higher levels of evidence include Opdivo (nivolumab), with or without concomitant Yervoy (ipilimumab), and Keytruda (pembrolizumab).
- Opdualag (nivolumab-relatlimab-rmbw) is not listed among the recommendation for:
    * Uveal melanoma (the pivotal trial excluded patients with uveal melanoma)
- Opdualag (nivolumab-relatlimab-rmbw) is now also listed as an option for subsequent-line therapy of advanced melanoma. NCCN guidelines recommend that, following progression or poor response, subsequent lines of therapy should use different mechanisms of action. At this time, there is no robust comparative clinical trial evidence to support the use of Opdualag after progression on previous therapy, and as such this use is considered investigational per this policy.

Reauthorization Criteria:

- When coverage criteria are met, Opdualag (nivolumab-relatlimab-rmbw) is authorized for six months (24 weeks) of therapy, after which time documentation must be provided to establish that the medication is effective. Specifically, there must be documentation of clinical benefit, including disease stability or improvement and there is a lack of disease progression, based on an assessment of change in tumor burden.
    * The standard of care for evaluation of response to cancer immunotherapy, such as Opdualag (nivolumab-relatlimab-rmbw) is use of the iRECIST criteria for assessment of tumor burden. [4]
    * The iRECIST criteria include use of quantitative and qualitative criteria for assessment of change in tumor burden for target lesions and non-target lesions. [5]
        - Quantitative measurements for target lesions (tumor size and % change)
        - Qualitative evaluation for non-target lesions (present/disappeared/ unequivocal progression)
    * Documentation of benefit must include an assessment of the most recent imaging ("restaging scans") by the treating oncologist. Given the complexity of the evaluation, including use of the iRECIST criteria, Opdualag (nivolumab-relatlimab-rmbw) will not be reauthorized without an assessment of response to therapy, such a partial response (iPR), complete response (iCR), or stable disease (iSD).
    * Use of immunotherapy may result in pseudoprogression, due to immune and T-cell activation, which can appear similar to tumor flare. If there is documentation of potential disease progression ["unconfirmed progressive disease (iUPD)"], a shortened authorization (up to three months) may be approved to allow time for clarification of response to Opdualag (nivolumab-relatlimab-rmbw), including clinical re-evaluation of the patient and reimaging. Guidelines recommend reimaging for iUPD after 4-8 weeks.
    * If a patient has confirmed, unequivocal new lesions (progression of disease, iPD), additional Opdualag (nivolumab-relatlimab-rmbw) is not coverable. If a new lesion is equivocal, iUPD reassessment by the treating oncologist with repeat imaging would apply (as noted above).

Investigational Uses [6]

- There is interest in using Opdualag (nivolumab-relatlimab-rmbw) in other tumors that express LAG-3; however, there are currently no well-controlled, published trials supporting its safety and efficacy in other cancers at this time.
- There is no evidence to support the use of Opdualag (nivolumab-relatlimab-rmbw) in combination with any other melanoma therapy.

Safety [7 8]

- Qualitatively, the adverse effects reported in the Opdualag (nivolumab-relatlimab-rmbw) clinical trial were similar to those reported with Opdivo (nivolumab). However, as relatlimab is a new entity and safety experience is limited, it cannot be ruled out that additional harms may become known in the future.

- Approximately one in two to three patients receiving Opdualag (nivolumab-relatlimab-rmbw) in the pivotal trial experienced a dose interruption, or permanent discontinuation due to AEs.

Dosing [7]

- Opdualag (nivolumab-relatlimab-rmbw) is intravenously administered every four weeks until disease progression.
- Opdualag is available in a fixed combination of nivolumab 240 mg and relatlimab 80 mg per 20 ml. The dose for patients with a weight of at least 40 kg is 480 mg/160 mg IV every 4 weeks until disease progression. No dose has been established for patients weighing less than 40 kg.

Appendix 1: FDA-approved PD-1 and PD-L1 blocking monoclonal antibody therapies [a]
Programmed death receptor-1 (PD-1) inhibitors
Jemperli (dostarlimab)
Keytruda (pembrolizumab)
Libtayo (cemiplimab-rwlc)
Loqtorzi (toripalimab)
Opdivo (nivolumab)
Tevimbra (tislelizumab)
Zynyz (retifanlimab-dlwr)
Programmed death-ligand 1 (PD-L1) inhibitor
Bavencio (avelumab)
Imfinzi (durvalumab)
Tecentriq (atezolizumab)

[a] Or as listed on the FDA.gov website

Cross References
Keytruda, pembrolizumab, Medication Policy Manual, Policy No. dru367
Opdivo, nivolumab, Medication Policy Manual, Policy No. dru390
Yervoy, ipilimumab, Medication Policy Manual, Policy No. dru238
Mitogen-activated extracellular signal-regulated kinase (MEK) Inhibitors [Cotellic (cobimetinib), Mektovi (binimetinib), trametinib (Mekinist)], Medication Policy Manual, Policy No. dru727
BRAF inhibitors [Braftovi (encorafenib), Tafinlar (dabrafenib), Zelboraf (vemurafenib)], Medication Policy Manual, Policy No. dru728

Cross References		
Codes	**Number**	**Description**
HCPCS	J9298	Injection, nivolumab and relatlimab-rmbw, 3 mg/1 mg

References

1. Tawbi HA, Schadendorf D, Lipson EJ, et al. Relatlimab and Nivolumab versus Nivolumab in Untreated Advanced Melanoma. *N Engl J Med.* 2022;386(1):24-34. PMID: 34986285
2. Ascierto PA, Lipson EJ, Dummer R, et al. Nivolumab and Relatlimab in Patients With Advanced Melanoma That Had Progressed on Anti-Programmed Death-1/Programmed Death Ligand 1 Therapy: Results From the Phase I/IIa RELATIVITY-020 Trial. *J Clin Oncol.* 2023;41(15):2724-35. PMID: 36780608
3. NCCN Drugs and Biologics Compendium (NCCN Compendium™) [Updated regularly] [cited with policy updates and as necessary]. 'Available from:' https://www.nccn.org/guidelines/category_1.
4. Seymour L, Bogaerts J, Perrone A, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. *Lancet Oncol.* 2017;18(3):e143-e52. PMID: 28271869
5. Persigehl, T., et al. (2020). iRECIST: how to do it. Cancer Imaging. England. **20:** 2.
6. National Institutes of Health, Clinicaltrials.gov [website]. [cited periodically]. 'Available from:' www.clinicaltrials.gov.
7. Opdualag (nivolumab and relatlimab-rmbw) [package insert]. Bristol-Myers Squibb Company; Princeton, NJ; March 2024.
8. Opdivo (nivolumab) [package insert]. Bristol-Myers Squibb Company; Princeton, NJ; March 2024.

Revision History

Revision Date	Revision Summary
9/19/2024	**Effective 1/1/2025:** Changed reauthorization from 'may' to 'shall.' Operationally, all approvals will be for 24 weeks (6 months). Ongoing therapy (beyond 24 weeks) will be subject to reauthorization review every 24 weeks, for documentation of disease stability or improvement and lack of disease progression.
9/19/2024	**Effective 12/1/2024:** • Clarification of coverage criterion "no prior systemic therapy in the advanced setting" to include "including but not limited to prior use of PD-1 inhibitors or PD-L1 inhibitors." • Addition of Investigational Uses, to include use as subsequent therapy in the advanced setting, as well as sequential PD1/PD-L1 therapy in the advanced setting.
9/14/2023	No criteria changes with this annual review.
12/9/2022	No changes to coverage criteria with this annual update.
06/17/2022	New Policy (effective 7/15/2022). • Limits coverage to patients with unresectable or metastatic melanoma when Opdualag (nivolumab-relatlimab-rmbw) is given as monotherapy and there has been no prior systemic therapy in the advanced disease setting. • Opdualag (nivolumab-relatlimab-rmbw) may be covered in doses up to 480 mg/160mg monthly, the dose studied in the pivotal trial and the maximum dose listed in the FDA label.

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Medication Policy Manual

Policy No: dru722

Topic: Pluvicto, lutetium Lu 177 vipivotide tetraxetan

Date of Origin: October 15, 2022

Committee Approval Date: June 20, 2024

Next Review Date: 2025

Effective Date: September 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Pluvicto (lutetium Lu 177 vipivotide tetraxetan) is an intravenously administered radiopharmaceutical approved for use in patients with a specific type of prostate cancer (prostate-specific membrane antigen [PSMA]-positive, metastatic castration-resistant prostate cancer [mCRPC]).

Policy/Criteria

Most contracts require pre-authorization approval of Pluvicto (lutetium Lu 177 vipivotide tetraxetan) prior to coverage.

I. Continuation of therapy (COT): Pluvicto (lutetium Lu 177 vipivotide tetraxetan) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, full policy criteria must be met for coverage.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Pluvicto (lutetium Lu 177 vipivotide tetraxetan) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A through D below are met:

A. A diagnosis of **metastatic castration-resistant prostate cancer** (mCRPC).

AND

B. Attestation that the metastatic lesions are predominantly prostate-specific membrane antigen (PSMA)-positive (no dominant PSMA-negative metastatic lesions).

AND

C. There has been disease progression on or after treatment with both of the following (1 and 2):

1. At least one androgen receptor pathway inhibitor (see *Appendix A*).

AND

2. At least one taxane-based chemotherapy regimen (see *Appendix B*).

AND

D. Testosterone levels are at castrate levels (< 50 ng/dL).

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Pluvicto (lutetium Lu 177 vipivotide tetraxetan) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Pluvicto (lutetium Lu 177 vipivotide tetraxetan) will be approved for up to a total of six of the 7.4 GBq infusions.

C. Authorization **may** be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, including disease stability or improvement relative to baseline symptoms.

IV. Pluvicto (lutetium Lu 177 vipivotide tetraxetan) is considered investigational when used for all other conditions.

Position Statement

Summary

- Pluvicto (lutetium Lu 177 vipivotide tetraxetan) is an intravenously administered radioligand that delivers radiation to prostate cancer cells that are positive for prostate-specific membrane antigen (PSMA).
- The intent of this policy is to allow coverage of Pluvicto (lutetium Lu 177 vipivotide tetraxetan) in the clinical setting described in the coverage criteria above, where it has been evaluated for efficacy, up to the dose shown to be safe in clinical trials.
- The FDA approval of Pluvicto (lutetium Lu 177 vipivotide tetraxetan) was based on a fair quality, randomized, controlled trial in patients with metastatic castration-resistant prostate cancer (mCRPC) with at least one PSMA-positive metastatic lesion (and no PSMA-negative lesions). Patients in the trial had progression of their disease on at least one prior androgen receptor pathway inhibitor and at least one prior taxane (docetaxel, cabazitaxel).
- As per standard of care, castrate levels of testosterone (< 50 ng/dL) were maintained throughout the study.
- In the pivotal study, Pluvicto (lutetium Lu 177 vipivotide tetraxetan) was found to improve median survival relative to best supportive care/standard of care.
- The current National Comprehensive Cancer Network (NCCN) prostate cancer guideline lists Pluvicto (lutetium Lu 177 vipivotide tetraxetan) among the recommendations for mCRPC when there is at least one PSMA-positive metastatic lesion and/or the disease is predominantly PSMA-positive and with no dominant PSMA-negative metastatic lesions, and there has been prior treatment with androgen receptor-directed therapy and a taxane-based chemotherapy regimen.

- Pluvicto (lutetium Lu 177 vipivotide tetraxetan) may be in doses of up to 7.4 GBq per infusion given every six weeks for a maximum of six infusions. The safety and efficacy of higher or more frequent doses have not been established.
- The safety and effectiveness of Pluvicto (lutetium Lu 177 vipivotide tetraxetan) in other conditions or in other prostate cancer settings have not been established.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy

- The efficacy of Pluvicto (lutetium Lu 177 vipivotide tetraxetan) was studied in a fair quality, open-label, randomized controlled trial in prostate-specific membrane antigen (PSMA)-positive, metastatic castrate-resistant prostate cancer (mCRPC) which compared it with best supportive care (BSC)/standard of care. [1,2]
    * Tumor histology in the enrolled population consisted of 91% with adenocarcinoma, and 1% with 'other' histology. Status was unknown in the remaining 8% of subjects.
    * All subjects had at least one PSMA-positive metastatic lesion, and no PSMA-negative metastatic lesions.
    * All subjects had at least one prior androgen receptor inhibitor (e.g., abiraterone, enzalutamide) and at least one prior taxane-based therapy (e.g., docetaxel, cabazitaxel).
    * Castrate levels of testosterone (< 50 ng/dL) were maintained throughout the study. Concomitant androgen blocking therapies included enzalutamide, abiraterone, and gonadotropin-releasing hormone (GNRH) analogues.

* Treatment was continued for up to 6 doses of Pluvicto (lutetium Lu 177 vipivotide tetraxetan) unless imaging-documented progression was detected prior to completion.

- The median OS was 15.3 months and 11.3 months in the Pluvicto (lutetium Lu 177 vipivotide tetraxetan) and BSC treatment arms, respectively. [2] There is some uncertainty in the results due to the very high rate of attrition in the BSC treatment arm; however, a relevant improvement in OS in favor or Pluvicto (lutetium Lu 177 vipivotide tetraxetan) appears to have been maintained based on follow up with missing subjects and several confirmatory sensitivity analyses. Accurate point estimates of expected survival benefit are difficult to determine because of this potential performance bias. [1]

Guideline recommendations [3]

- The current National Comprehensive Cancer Network (NCCN) prostate cancer guideline lists Pluvicto (lutetium Lu 177 vipivotide tetraxetan) as a category 1 recommendation for mCRPC when there is at least one PSMA-positive metastatic lesion and/or the disease is predominantly PSMA-positive and with no dominant PSMA-negative metastatic lesions, and there has been prior treatment with androgen receptor-directed therapy and a taxane-based chemotherapy regimen.
- The guideline recommends continuation of androgen deprivation therapy in the mCRPC population to keep testosterone at castrate levels (< 50 ng/dL).

Investigational Uses [4]

- There were no additional studies for Pluvicto (lutetium Lu 177 vipivotide tetraxetan) identified in clinicaltrials.gov.
- There is a small risk that Pluvicto (lutetium Lu 177 vipivotide tetraxetan) might be used in patients that do not have “predominantly PSMA-positive metastatic lesions” depending on the location of the given metastases.

Safety [1,5]

- Pancytopenia, fatigue, urinary tract infection, and kidney injury are the primary adverse effects experienced with Pluvicto (lutetium Lu 177 vipivotide tetraxetan).
- Renal function should be carefully monitored in patients receiving Pluvicto (lutetium Lu 177 vipivotide tetraxetan). Patients should remain adequately hydrated while receiving therapy.

Dosing [5]

- Pluvicto (lutetium Lu 177 vipivotide tetraxetan) should be administered at a facility that is licensed to handle radiopharmaceuticals.
- The recommended dose of Pluvicto (lutetium Lu 177 vipivotide tetraxetan) is 7.4 GBq (200 mCi) intravenously every six weeks for up to six total infusions, or until disease progresses, whichever comes first.

Appendix A: Androgen Receptor Pathway Inhibitors Approved for Use in Castration-Resistant Prostate Cancer (CRPC)
abiraterone (Zytiga, Yonsa)
Erleada (apalutamide)
Nubeqa (darolutamide)
Xtandi (enzalutamide)

Appendix B: Taxanes Used in the Treatment of Prostate Cancer
docetaxel (generic, Taxotere)
cabazitaxel (generic, Jevtana)

Cross References
BlueCross BlueShield Association Medical Policy, 5.01.43 - Therapeutic Radiopharmaceuticals for Prostate Cancer. [September 2023]

Codes	Number	Description
HCPCS	A9607	Lutetium lu 177 vipivotide tetraxetan (Pluvicto), therapeutic, 1 millicurie

References

1. Center for Drug Evaluation and Research; U.S. Food and Drug Administration Multi-Discipline Review, NDA 215-833; ^{177}Lu-PSMA-617 (Pluvicto™). [cited 5/26/2022]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/215833Orig1s000MultidisciplineR.pdf.
2. Sartor O, de Bono J, Chi KN, et al. Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. *N Engl J Med*. 2021;385(12):1091-103. PMID: 34161051
3. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology™. [Updated routinely]. [cited with policy updates and as necessary]. Available from: https://www.nccn.org/guidelines/category_1.
4. National Institutes of Health, Clinicaltrials.gov [website]. [cited periodically]. Available from: www.clinicaltrials.gov.
5. Pluvicto® (lutetium Lu 177 vipivotide tetraxetan) [package insert]. Novartis Pharmaceuticals Corporation; East Hanover, NJ; October 2022.

Revision History

Revision Date	Revision Summary
6/20/2024	No criteria changes with this annual review.
12/7/2023	No criteria changes with this annual review.
12/9/2022	No changes to criteria with this annual update.
9/23/2022	New Policy (effective 10/15/2022). • Limits coverage of Pluvicto (lutetium Lu 177 vipivotide tetraxetan) to metastatic castration-resistant prostate cancer (mCRPC) when metastatic lesions are predominantly PSMA-positive (no dominant PSMA-negative lesions), there has been disease progression on at least one prior androgen receptor pathway inhibitor AND at least one taxane-based chemotherapy regimen, and castrate levels of testosterone are maintained. • Pluvicto (lutetium Lu 177 vipivotide tetraxetan) may be covered in doses up to 7.4GBq per infusion for up to a total of six infusions, or until there is radiographic disease progression.

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Medication Policy Manual **Policy No:** dru733

Topic: Medications for transthyretin-mediated amyloidosis

Date of Origin: January 15, 2023

- Amvuttra, vutrisiran
- Onpattro, patisiran
- Tegsedi, inotersen
- Vyndamax, tafamidis
- Vyndaqel, tafamidis meglumine
- Wainua, eplontersen

Committee Approval Date: June 20, 2024 **Next Review Date:** 2025

Effective Date: September 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Medications included in this policy are used for the treatment of transthyretin mediated (ATTR) amyloidosis, which is a rare, progressive disease that can affect the nervous system, heart, and other major organs.

Policy/Criteria

Most contracts require pre-authorization approval of medications for ATTR amyloidosis prior to coverage.

I. Continuation of therapy (COT): Medications for ATTR amyloidosis may be considered medically necessary for COT when criterion A **AND** B below are met.

A. One of the following (1, 2, or 3)

1. For diagnoses NOT listed in the coverage criteria below, full policy criteria must be met for coverage.

OR

2. For diagnoses listed in the coverage criteria below, criteria a. and b. must be met:

a. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

b. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

3. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission

AND

B. **For Amvuttra and Onpattro only (effective 10/1/2024)**: Site of care administration requirements are met [refer to Medication Policy Manual, Site of Care Review, dru408].

Please note: *Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Medications for ATTR amyloidosis may be considered medically necessary when criterion A **AND** B below are met.

A. One of the following diagnostic criteria are met (1 or 2)

1. **Hereditary transthyretin (hATTR) amyloidosis with polyneuropathy: Amvuttra (vutrisiran), Onpattro (patisiran), Tegsedi (inotersen), or Wainua (eplontersen)** may be considered medically necessary for hATTR with polyneuropathy when there is clinical documentation (including, but not limited to chart notes) that criteria a through e below are met.

a. A diagnosis of **hereditary transthyretin (hATTR) amyloidosis with polyneuropathy** established by a specialist in neurology, cardiology, amyloidosis, or genetics.

AND

b. The diagnosis has been confirmed by genetic testing, with documentation of a mutation in the transthyretin (TTR) gene.

AND

c. The patient has impairment due to neuropathy with a **Polyneuropathy Disability** (PND) score between I-IIIb or are in **Familial Amyloid Polyneuropathy** (FAP) Stage 1 or Stage 2 (as defined in *Appendix 1*).

AND

d. The patient has symptoms consistent with polyneuropathy (see *Appendix 2*).

AND

e. **For Tegsedi (inotersen) and Wainua (eplontersen) only:** The patient has not had a prior liver transplant.

OR

2. **Cardiomyopathy of transthyretin-related amyloidosis (ATTR-CM): Vyndamax (tafamidis) or Vyndaqel (tafamidis meglumine)** may be considered medically necessary for ATTR-CM when there is clinical documentation (including, but not limited to chart notes) that criteria a through d below are met.

a. A diagnosis of wild-type or hereditary **cardiomyopathy of transthyretin-related amyloidosis** (ATTR-CM) was established in consultation with a specialist in cardiology.

AND

b. The diagnosis has been confirmed by biopsy, immunohistochemical analysis, scintigraphy, or mass spectrometry.

AND

c. Documented New York Heart Association (NYHA) functional class I, II, or III.

AND

d. The patient has not had a liver and/or heart transplant.

AND

B. **For Amvuttra and Onpattro only (effective 10/1/2024)**: Site of care administration requirements are met [refer to Medication Policy Manual, Site of Care Review, dru408].

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Amvuttra (vutrisiran) and Onpattro (patisiran) coverable only under the medical benefit (as provider-administered medications).

B. Regence Pharmacy Services considers Tegsedi (inotersen), Vyndamax (tafamidis), Vyndaqel (tafamidis meglumine), and Wainua (eplontersen) coverable only under the pharmacy benefit (as self-administered medications).

C. When pre-authorization is approved, medications for ATTR amyloidosis will be authorized in the following quantities and for the following authorization periods outlined in *Table 1* below.

Table 1 Medications for ATTR amyloidosis

Authorization Limits
Polyneuropathy of hATTR amyloidosis: - Amvuttra (vutrisiran): Up to 4 injections of a 25 mg prefilled syringe in a one-year period. - Onpattro (patisiran): Patients < 100kg: Up to 18 infusions in a one-year period based on dose of 0.3 mg/kg every 3 weeks. Patients ≥ 100kg: Up to 18 infusions in a one-year period based on a dose of 30 mg every 3 weeks. - Tegsedi (inotersen): Up to 4 prefilled syringes per 28 days. - Wainua (eplontersen): Up to one autoinjector per 28 days. Authorization **shall** be reviewed at least every twelve months. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met as and that the medication is providing clinical benefit, including stability or improvement in symptoms consistent with polyneuropathy.
Cardiomyopathy of transthyretin-related amyloidosis (ATTR-CM): - Vyndamax (tafamidis): Up to 30 of the 61 mg tablets per 30 days. - Vyndaqel (tafamidis meglumine): Up to 120 of the 20 mg tablets per 30 days. Authorization **shall** be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability, improvement in heart failure symptoms, or improvement of NYHA functional class.

IV. Medications for ATTR amyloidosis are considered investigational when used for all other conditions, including but not limited to:

A. In combination with another medication for ATTR amyloidosis (as listed in this policy).

B. Other forms of amyloidosis not specified above.

Position Statement

Summary

- Medications for transthyretin-mediated (ATTR) amyloidosis may be covered for specific diagnoses where there is demonstrated safety and efficacy from randomized, controlled trials to support their use, including treatment of polyneuropathy hereditary transthyretin-mediated amyloidosis (hATTR) and treatment of cardiomyopathy of wild-type or hereditary transthyretin-mediated amyloidosis.
    - Small interfering RNA (siRNA) medications including Amvuttra (vutrisiran) and Onpattro (patisiran) silence the transthyretin (TTR) gene resulting in a reduction of serum and tissue TTR concentrations.
    - Tegsedi (inotersen) and Wainua (eplontersen) are RNA oligonucleotides that work by silencing the TTR gene resulting in a reduction of serum and tissue TTR concentrations.
    - Tafamidis is a transthyretin (TTR) stabilizer that selectively binds to specific sites of the TTR tetramer to prevent destabilization and amyloid fibril formation.

- Medications for ATTR amyloidosis may be covered at the doses proven to be safe and effective in the clinical trials (as outlined in *Table 1* of the coverage criteria above). The safety and effectiveness of higher doses has not been established. Use of medications for ATTR amyloidosis in clinical settings other than described in the coverage criteria is considered investigational.
- The safety and efficacy of medications for ATTR amyloidosis being used in combination with each other has not been established and is considered investigational.

Polyneuropathy of hATTR Amyloidosis

- Medications for polyneuropathy of hATTR amyloidosis are intravenous (IV) or subcutaneously administered medications and include the following: Onpattro (patisiran), Amvuttra (vutrisiran), Wainua (eplontersen), and Tegsedi (inotersen).
- The intent of the policy is to allow coverage of medications for polyneuropathy of hATTR amyloidosis in patients with a confirmed diagnosis of hATTR (by genetic testing), when there is documented symptomatic impairment due to polyneuropathy, similarly to how it was studied, as detailed in the coverage criteria.
- The effectiveness of the medications for polyneuropathy of hATTR amyloidosis were demonstrated in phase 3 randomized, controlled trials, in patients with genetically confirmed hATTR amyloidosis and symptomatic polyneuropathy, familial amyloidosis polyneuropathy (FAP) Stage 1 or 2.
- All medications for polyneuropathy of hATTR amyloidosis slowed the progression of neurologic worsening and decline in quality of life compared to placebo. In addition, Onpattro (patisiran), Amvuttra (vutrisiran), and Wainua (eplontersen) improved neurologic function and quality of life compared to placebo.
- Genetic testing is required to confirm the diagnosis of hATTR amyloidosis.
- Patients with a history of liver transplant were excluded from pivotal trials; however, a more recent study of Onpattro (patisiran) did show similar efficacy in patients with previous liver transplant.
- There is insufficient evidence that any one medication for the treatment of polyneuropathy in hATTR is superior to another as there are currently no comparative trials.
- Tegsedi (inotersen) is associated with severe, potentially fatal adverse effects (thrombocytopenia, glomerulonephritis, hepatotoxicity, and neurologic reactions) and has a REMS program.

Cardiomyopathy of transthyretin-related amyloidosis (ATTR-CM)

- The intent of this policy is to limit coverage of medications for ATTR-CM hATTR amyloidosis in patients with a confirmed diagnosis of ATTR-CM and to ensure use similarly to how they were studied, as detailed in the coverage criteria.
- The efficacy of tafamidis was established based on one clinical trial in adults with ATTR-CM (wild-type or hereditary). Tafamidis improved all-cause mortality and reduced cardiovascular (CV)-related hospitalizations at 30 months as compared to placebo.
- A biopsy is the gold standard for confirming a diagnosis of ATTR-CM. Other less invasive methods include immunohistochemical analysis, scintigraphy, or mass spectrometry.

- Subjects with a liver and/or heart transplant were excluded from clinical trial. It is unclear if patients with a prior liver and/or heart transplant who use tafamidis-containing medications will receive clinical benefit.
- Patients with NYHA class IV functional status who were unlikely to benefit from the medication were excluded from the study.
- Vyndaqel (tafamidis meglumine) 80 mg and Vyndamax (tafamidis) 61 mg are bioequivalent.

Clinical Efficacy

Polyneuropathy of hATTR Amyloidosis

Background [1-7]

- hATTR amyloidosis is a rare, rapidly progressing condition, caused by an autosomal-dominant inherited mutation in the TTR gene resulting in misfolded protein accumulating as amyloid fibrils in nerves, heart, gastrointestinal tract, or other tissues, leading to progressive disability and loss of function in major organs presenting as neurological, cardiac, or mixed phenotype.
- Neurologic phenotype, also known as familial amyloid polyneuropathy (FAP), manifests as sensorimotor polyneuropathy with a high variability in symptoms impacting quality of life such as pain, numbness, muscle weakness, weight loss/wasting, focal nerve lesions, and autonomic dysfunction, while patients with a cardiac phenotype experience cardiomyopathy leading to heart failure.
- Symptom onset can occur anywhere between the ages of 20-70, is often misdiagnosed without family history of disease, and can only be confirmed with biopsy and genetic confirmation of the TTR mutation.
- Life expectancy once diagnosed is between 5-12 years, though often shorter in patients with cardiomyopathy, with death attributed to cardiac dysfunction, infection, and cachexia.
- There are no consensus U.S. treatment guidelines. However, the 2022 Canadian Neurological Sciences Foundation guidelines now recommend Onpattro (patisiran) and Tegsedi (inotersen) as first line agents. Guidelines have not been updated since the approval of the newer TTR lowering medications (Amvuttra and Wainua).
- Liver transplant was the previous standard of care in early disease but does not prevent progression as the wild type TTR may continue to expand amyloid deposits and is no longer recommended as first line treatment.
- Vyndamax/Vyndaqel (tafamidis) and diflunisal stabilize TTR protein and are sometimes used in this indication; however, they have not been FDA approved. Tafamidis failed to receive approval from FDA for this indication due to not meeting statistical significance and diflunisal does not reverse course of disease and has limitations due to long term risks of adverse effects.
- Endpoints in trials included modified Neuropathy Impairment Score +7 (mNIS+7) and in the Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QOL-DN). [8 9]
    * The mNIS+7 is an exam-based assessment of neuropathy which includes measures of nerve fiber conduction, sensory testing, and autonomic measures (postural blood pressure). Higher scores indicate worse neurologic function.

* The Norfolk QOL-DN evaluates patients' perception of impairment with respect to physical functioning/large fiber neuropathy, activities of daily living, neuropathy symptoms, small fiber neuropathy, and autonomic dysfunction. Higher scores indicate poorer quality of life.

Tegsedi (inotersen)[10]

- Efficacy of Tegsedi (inotersen) was demonstrated the NEURO-TTR study, a 15-month, phase 3 randomized, placebo-controlled trial. [10] Patients were required to meet the following requirements for enrollment:
  * FAP stage 1 (ambulatory) or stage 2 (ambulatory with assistance).
  * A diagnosis of hATTR confirmed by genetic testing and biopsy.
  * Symptoms of neuropathy measured using the Neuropathy Impairment Score (NIS). The NIS is a tool used to measure motor, sensory, and reflex function.
  * Patients with a history of liver transplant were excluded.
- The primary endpoints in modified Neuropathy Impairment Score +7 (mNIS+7) and in the Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QOL-DN).
- Results showed that Tegsedi (inotersen) slowed the progression of neurologic symptoms and decline in quality of life compared to placebo. There is limited data on cardiovascular outcomes or mortality.
- Trials for Tegsedi (inotersen) excluded patients:
  * with prior liver transplant. At this time, it is unclear if patients who have received a liver transplant would experience benefit from these medications.
  * that were on TTR stabilizers such as Vyndamax/Vyndaqel (tafamidis) or diflunisal. At this time, it is unclear if patients receiving concomitant use of medications for hATTR with polyneuropathy and TTR stabilizers above is safe or effective.
  * Use of Tegsedi (inotersen) is investigational in these patient populations.

Onpattro (patisiran) [1 11-13]

- Efficacy of Onpattro (patisiran) was demonstrated the APOLLO study, an 18-month, phase 3 randomized, placebo-controlled trial. Patients were required to meet the following requirements for enrollment:
  * FAP stage 1 (mild ambulatory impairment) or stage 2 (ambulatory with assistance).
  * A diagnosis of hATTR confirmed by genetic testing and biopsy.
  * Symptoms of neuropathy measured using the Neuropathy Impairment Score (NIS). The NIS is a tool used to measure motor, sensory, and reflex function.
  * Patients with a history of liver transplant were excluded.
- The primary endpoint was change in modified Neuropathy Impairment Score +7 (mNIS+7) from baseline. Change in Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QOL-DN) score was a secondary endpoint.
- Results showed that Onpattro (patisiran) improved neurologic symptoms and improved quality of life compared to placebo. There is limited data on effect of Onpattro (patisiran) on other end organ dysfunction associated with amyloidosis, such as cardiovascular outcomes or mortality.

- A recent phase 3b open-label, single arm trial (n=23) demonstrated efficacy of Onpattro (patisiran) in patients post liver transplant.
    * Patients had received a liver transplant 12 months prior to study, and had experienced polyneuropathy progression post-transplant, defined as an increase of PND.
    * PND scores of IV were excluded from the trial, as well as past use of Onpattro (patisiran) or Tegsedi (inotersen).
- The primary endpoint of serum TTR reduction showed statistically significant reduction with the median percent reduction from baseline at 12 months of 91%. Secondary endpoints of mean improvements from baseline of neurological impairment score (NIS) of -3.7 and Norfolk QOL-DN of -6.5, support the primary endpoints and are in line with the results from the primary APOLLO trial for which Onpattro (patisiran) previously was approved.
- Trials for Onpattro (patisiran) excluded patients that were on TTR stabilizers such as Vyndamax/Vyndaqel (tafamidis) or diflunisal. At this time, it is unclear if patients receiving concomitant use of medications for hATTR with polyneuropathy and TTR stabilizers above is safe or effective. Use of Onpattro (patisiran) is investigational in these patient populations.

Amvuttra (vutrisiran) [4 14 15]

- Efficacy of Amvuttra (vutrisiran) was demonstrated the HELIOS-A study, an 18-month, phase 3 randomized, externally placebo-controlled trial.
    * Patients were required to meet the following requirements for enrollment:
        - A diagnosis of hATTR confirmed by presence of a TTR gene mutation.
        - Polyneuropathy disability (PND) score between I-IIIb, which equates to being FAP stage 1 (mild ambulatory impairment) or stage 2 (ambulatory with assistance).
        - Symptoms of neuropathy measured using the Neuropathy Impairment Score (NIS) scoring between 5-130. The NIS is a tool used to measure motor, sensory, and reflex function.
        - Patients with a history of liver transplant were excluded.
        - Patients treated with TTR stabilizers (tafamidis or diflunisal) must have been off therapy for 14 days prior to enrollment to be included.
    * Patients were randomized 3:1 to be treated with Amvuttra (vutrisiran) 25 mg every 3 months or a reference comparator Onpattro 0.3 mg/kg every 3 weeks, respectively for 18 months.
    * Efficacy data was determined by comparing the Amvuttra (vutrisiran) population (n=122) of the HELIOS-A trial to the external placebo group (n=77) from the APOLLO trial above, (for which Onpattro [patisiran] received FDA approval when compared to the same placebo group).
    * The inclusion/exclusion criteria and endpoints from the external placebo group in the APOLLO trial were the same in the HELIOS-A trial.
    * Baseline characteristics were similar between groups, however in the APOLLO trial, patients appeared to have more severe disease compared to the HELIOS-A trial with a baseline mNIS+7 of 74.6 vs 60.6, and Norfolk QOL-DN total score 55.5 vs 47.1, respectively.
    * The primary endpoint was the mean change in modified Neuropathy Impairment

Score +7 (mNIS+7) from baseline at 9 months. Mean change in Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QOL-DN) score and the 10-meter walk test (10-MWT) were secondary endpoints at 9 and 18 months (mNIS+7 was also a secondary endpoint at 18 months).

  * Results showed that Amvuttra (vutrisiran) improved neurologic symptoms (mNIS+7 change from baseline was -2.2 in Amvuttra (vutrisiran) arm vs 14.76 in placebo at 9 months; -0.46 vs 28.09 at 18 months), quality of life (change from baseline in Norfolk QOL-DN was a -3.3 vs 12.9 compared to placebo at 9 months; -1.2 vs 19.8 at 18 months), and gait speed (change from baseline in 10-MWT was -.133 vs 0 compared to placebo at 9 months; -.264 vs -.02 at 18 months).

- There is currently no data on effect of Amvuttra (vutrisiran) on other end organ dysfunction associated with amyloidosis, such as cardiovascular outcomes or mortality.
- Use of an external placebo vs active comparator and the external placebo having more severe baseline disease are of a concern, however patients in the Amvuttra (vutrisiran) arm showed large statistical significance across all endpoints at 9 and 18 months compared to placebo, results were seen across all subgroups, and the disease did not follow the normal course of progression.
- Amvuttra (vutrisiran) also showed non-inferiority when looking at exploratory endpoints comparing the serum concentrations of TTR protein to the active comparator group of Onpattro (patisiran) patients at 18 months.
- Trials for Amvuttra (vutrisiran) excluded patients:
  * That were on TTR stabilizers such as Vyndamax/Vyndaqel (tafamidis) or diflunisal. At this time, it is unclear if patients receiving concomitant use of medications for hATTR with polyneuropathy and TTR stabilizers above is safe or effective.
  * Use of Amvuttra (vutrisiran) is investigational in these patient populations.

Wainua (eplontersen)[16-18]

- Efficacy of Wainua (eplontersen) was demonstrated the NEUROTTRansform study, a 66-week, phase 3 randomized, externally placebo-controlled trial.
  * Patients were required to meet the following requirements for enrollment:
    - A diagnosis of hATTR confirmed by presence of a TTR gene mutation.
    - Polyneuropathy disability (PND) score between I-IIIb, which equates to being FAP stage 1 (mild ambulatory impairment) or stage 2 (ambulatory with assistance).
    - Symptoms of neuropathy measured using the Neuropathy Impairment Score (NIS) scoring between 10-130. The NIS is a tool used to measure motor, sensory, and reflex function.
    - Patients with a history of liver transplant were excluded.
    - Patients treated with TTR stabilizers (tafamidis or diflunisal) must have been off therapy for 14 days prior to enrollment to be included.
  * Patients were randomized 6:1 to be treated with Wainua (eplontersen) 45 mg every month or a reference comparator Tegsedi (inotersen) 300 mg weekly, respectively for 35 weeks, with all patients transferred over to Wainua (eplontersen) from week 36 on.
  * Efficacy data was determined by comparing the Wainua (eplontersen) population (n=140) of the NEUROTTRansform trial to the external placebo group (n=59)

from the NEUROTTR trial above, (for which Tegsedi [inotersen] received FDA approval when compared to the same placebo group).
    * The inclusion/exclusion criteria and endpoints from the external placebo group in the NEUROTTR trial were the same in the NEUROTTRansform trial.
    * Baseline characteristics were similar between groups, however in the NEUROTTR trial, patients appeared to have less severe disease compared to the NEUROTTRansform trial with a baseline mNIS+7 of 74.8 vs 81.3, respectively.
    * The primary efficacy endpoints were the mean change in modified Neuropathy Impairment Score +7 (mNIS+7) from baseline at 35 and 66 weeks. Mean change in Norfolk Quality of Life-Diabetic Neuropathy (Norfolk QOL-DN) score was the pivotal secondary endpoint at 35 and 66 weeks.
    * Results showed that Wainua (eplontersen) improved neurologic symptoms (mNIS+7 change from baseline was 0.2 in Wainua (eplontersen) arm vs 9.2 in placebo at 35 weeks; 0.3 vs 25.1 at 66 weeks), quality of life (change from baseline in Norfolk QOL-DN was -3.1 vs 8.7 compared to placebo at 35 weeks:-5.5 vs 14.2 at 66 weeks).
    * Use of an external placebo vs active comparator confounds interpretation of the results; however, patients in the Wainua (eplontersen) arm showed large statistical significance across all endpoints at 35 and 66 weeks compared to placebo, results were seen across all subgroups, and the disease did not follow the normal course of progression.
- The trial for Wainua (eplontersen) excluded patients:
    * That were on TTR stabilizers such as Vyndamax/Vyndaqel (tafamidis) or diflunisal. At this time, it is unclear if patients receiving concomitant use of medications for hATTR with polyneuropathy and TTR stabilizers above is safe or effective.
- Use of Wainua (eplontersen) is investigational in these patient populations. There is currently no data on effect of Wainua (eplontersen) on other end organ dysfunction associated with amyloidosis, such as cardiovascular outcomes or mortality.

Cardiomyopathy of transthyretin-related amyloidosis (ATTR-CM)

Background [19 20]

- ATTR-CM is a rare, late-onset, life-threatening disease associated with restrictive cardiomyopathy and progressive heart failure. It is caused by the deposition of misfolded transthyretin (TTR) protein in the heart tissues that leads to the formation amyloid fibrils. Formation of amyloid fibrils leads to organ damage and dysfunction.
- ATTR-CM typically manifests as heart failure, characterized by dyspnea, edema, syncope, sudden cardiac death, pericardial disease, thromboembolism, stroke, and peripheral neuropathy.
- The diagnosis of cardiac amyloidosis is confirmed by a cardiac biopsy. Other non-invasive methods include nuclear scintigraphy and cardiac MRI.
- The prevalence is estimated to be 45 in 100,000. The number of newly diagnosed cases is expected to increase in the next five years due increased disease awareness and diagnosis. ATTR-CM can be hereditary or non-hereditary. The age of onset for hereditary (mutant) ATTR-CM is typically between 50 and 60, while wild-type typically occurs between ages 60 and 70.

- Median survival without treatment is reported to be 2.5 to 3.5 years after diagnosis. However, the evidence for the natural history of ATTR-CM is limited to small trials.
- Treatment is divided into management of heart failure symptoms (e.g. edema, dyspnea, risk of thromboembolism) and treatment of the underlying disease, with a liver transplant and tafamidis being the only treatments for underlying disease.
- A liver transplant is only indicated in hereditary ATTR-CM and was the previous standard of care but does not prevent progression as the wild type TTR may continue to expand amyloid deposits. A combined liver and heart transplant may be indicated for some patients with advanced heart disease.

Vyndaqel (tafamidis meglumine) and Vyndamax (tafamidis) [19 20]

- The efficacy of Vyndaqel (tafamidis meglumine) was established in a single 30-month phase 3, placebo-controlled, randomized-controlled trial (ATTR-ACT).
    * In the primary analysis, Vyndaqel (tafamidis meglumine) demonstrated an improvement in survival rates and reduction in CV-related hospitalizations in patients with ATTR-CM as compared to placebo.
    * Subjects were included in the study if they had a diagnosis of wild-type or hereditary ATTR-CM and a history of heart failure which required additional treatment (e.g. hospitalization, diuretics).
    * Subjects with NYHA class IV functional class had a previous liver and/or heart transplant, or had an implanted cardiac device were excluded from the trial. It is unclear if these patients will receive clinical benefit from Vyndaqel (tafamidis meglumine).
- In a bioequivalence study, Vyndaqel (tafamidis meglumine) 80 mg and Vyndamax (tafamidis) 61 mg demonstrated no clinically significant pharmacokinetic differences.
- Trials of Vyndaqel (tafamidis meglumine) excluded patients with prior liver and/or heart transplant. There are no published clinical trials evaluating the safety or efficacy of tafamidis-containing medications for the treatment of ATTR-CM in patient with prior liver and/or heart transplant.

Safety [2]

- Tegsedi (inotersen) is associated with severe, potentially fatal adverse effects. It contains boxed warning for thrombocytopenia and glomerulonephritis. Due to these serious safety concerns enrollment in the TEGSEDI REMS program is required prior to initiating treatment.

Appendix 1: Staging of hATTR amyloidosis with polyneuropathy [5 6]		
FAP Stage	Symptoms	Modified Polyneuropathy Disability (PND) Score

0	Asymptomatic	N/A
I	Mild, ambulatory, symptoms at lower limbs limited	I. Sensory disturbances in extremities but preserved walking capacity II. Difficulties in walking but without the need for a walking stick
II	Moderate, further neuropathic deterioration, ambulatory but requires assistance	IIIa. One stick or one crutch required for walking IIIb. Two sticks or two crutches required for walking
III	Severe, bedridden/wheelchair bound with generalized weakness	IV. Patient confined to a wheelchair or bed

Appendix 2: Symptoms of Polyneuropathy [4]	
Peripheral sensorimotor polyneuropathy Symptoms	**Autonomic neuropathy symptoms**
Tingling or increased pain in the hands, feet, hands and/or arms,	Orthostasis
Loss of feeling in the hands and/or feet, numbness or tingling in the wrists,	Abnormal sweating
Loss of ability to sense temperature,	Sexual dysfunction
Difficulty with fine motor skills	Recurrent urinary tract infections
Seizures	Dysautonomia (constipation and/or diarrhea, nausea, vomiting, anorexia, early satiety)

Cross References
Treatment of Hereditary Transthyretin-Mediated Amyloidosis in Adult Patients, BlueCross BlueShield Association (BCBSA) Medical Policy, MPRM5.01.30; Issue 1:2024.
Site of Care Review, Medication Policy Manual, Policy No. dru408

Codes	**Number**	**Description**
HCPCS	J0222	Injection, patisiran (Onpattro), 0.1 mg.
HCPCS	J0225	Injection, vutrisiran (Amvuttra), 1 mg

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Revision History

Revision Date	Revision Summary
6/20/2024	▪ Added newly FDA-approved drug Wainua (eplontersen) for polyneuropathy of hATTR amyloidosis in patients with a confirmed diagnosis of hATTR (by genetic testing), when there is documented symptomatic impairment due to polyneuropathy, similarly to how it was studied, as detailed in the coverage criteria (effective 9/1/2024). ▪ Added Amvuttra and Onpattro to site of care (SOC) program (effective 10/1/2024).
3/21/2024	No criteria changes with this annual review.
12/7/2023	No criteria changes with this annual review.
12/9/2022	New combination policy (effective 1/15/2023): ▪ Combined the following medication policies: dru577 Onpattro, patisiran, dru579 Tegsedi, inotersen, and dru595 tafamidis-containing medication; no change to intent of pre-existing criteria. ▪ Added newly FDA-approved drug Amvuttra (vutrisiran), for polyneuropathy of hATTR amyloidosis in patients with a confirmed diagnosis of hATTR (by genetic testing), when there is documented symptomatic impairment due to polyneuropathy, similarly to how it was studied, as detailed in the coverage criteria ▪ Removed requirement for "no prior liver transplant" for Onpattro (patisiran). ▪ For polyneuropathy criteria: - Clarified intent of "functional impairment" criterion to "symptomatic impairment" based on trial data and staging of polyneuropathy. - Removed Onpattro (patisiran) from "no previous liver transplant" criterion.

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Medication Policy Manual **Policy No:** dru735

Topic: Gene therapies for hemophilia B **Date of Origin:** January 15, 2023

- Hemgenix, etranacogene dezaparvovec-drlb
- Beqvez, fidanacogene elaparvovec-dzkt

Committee Approval Date: June 20, 2024 **Next Review Date:** 2025

Effective Date: July 15, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Medications in this policy are intravenous (IV) gene therapies used for the treatment of patients with hemophilia B.

Policy/Criteria

Most contracts require pre-authorization approval of gene therapies for hemophilia B prior to coverage.

I. Gene therapies for hemophilia B are considered investigational, except for those situations specifically addressed in the policy criteria below.

PLEASE NOTE: Under this criterion, any gene therapies for hemophilia B not specifically addressed in this policy will be considered investigational.

II. Continuation of therapy (COT): Gene therapies for hemophilia B may be considered medically necessary when full policy criteria below are met, including quantity limit. However, gene therapies for hemophilia B are not coverable for repeated doses and are not coverable if a patient has previously received prior gene therapy for hemophilia B.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

III. New starts (treatment-naïve patients): Gene therapies for hemophilia B may be considered medically necessary for the treatment of patients with severe hemophilia B when there is clinical documentation (including, but not limited to chart notes) that all criteria (A through J) below are met:

A. A diagnosis of **hemophilia B (congenital FIX deficiency),** established by or in consultation with a hematologist with experience treating hemophilia B.

AND

B. Confirmation of severe or moderate-severe phenotype (factor IX activity ≤ 2% of normal.)

AND

C. Laboratory confirmation showing that the patient does not have factor IX inhibitors (less than 0.6 Bethesda Units).

AND

D. The patient has been appropriately evaluated for and does not have any comorbidity which presents a significant safety risk (See *Appendix 1*).

AND

E. The patient does not have any medical contraindications to corticosteroids **(physician attestation).**

AND

F. The patient is ≥ 18 years of age.

AND

G. Patient has not received prior treatment with a gene therapy for hemophilia B.

AND

H. Routine prophylaxis with fully optimized dosing of exogenous factor IX has been ineffective, defined as having one of the following while taking optimized exogenous factor IX prophylaxis (1 or 2):

1. Repeated bleeding episodes requiring acute treatment with additional doses of exogenous blood factor (factor IX) while taking optimized prophylaxis.

OR

2. Documentation of progressive disability including, but not limited to, disability from arthropathy due to bleeding.

AND

I. ***For Hemgenix (etranacogene dezaparvovec-drlb) only***: Laboratory confirmation showing that the patient is negative for antibodies to AAV5 (anti-AAV5 antibodies) or having anti-AAV5 titers ≤ 679.

AND

J. ***For Beqvez (fidanacogene elaparvovec-dzkt) only:*** Laboratory confirmation showing that the patient is negative for antibodies to AAVRh74 var (anti-AAVRh74 antibodies).

IV. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers gene therapies for hemophilia B coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, gene therapies for hemophilia B may be authorized in quantities of one treatment course per lifetime.

C. Additional infusions of gene therapies for hemophilia B will not be authorized.

V. Use of gene therapies for hemophilia B in patients who are successfully managed with prophylactic exogenous factor IX replacement therapy is considered "not medically necessary".

VI. Investigational Uses

A. Repeated doses gene therapies for hemophilia B, including for gene therapies for hemophilia B previously given as part of a clinical trial.

B. Unless otherwise specified in the coverage criteria above, gene therapies for hemophilia B are considered investigational when used for all other conditions.

Position Statement

Summary

- Hemophilia B is a rare X-linked congenital bleeding disorder caused by a deficiency of coagulation factor IX (FIX), part of the intrinsic coagulation pathway. A deficiency in circulating FIX leads to impaired clotting and bleeding episodes.
- Gene therapies for hemophilia B are FDA approved adeno-associated viral (AAV) vector-based intravenous (IV) medications, that replace the defective FIX gene and include:
    * Hemgenix (etranacogene dezaparvovec-drlb), which uses a AAV5 vector.
    * Beqvez (fidanacogene elaparvovec-dzkt), which uses a AAVRh74 vector.
- The intent of this policy is to allow for coverage of gene therapies for hemophilia B in patients with severe hemophilia, that are clinically fit for gene therapy treatment, for whom routine optimized prophylactic exogenous factor IX therapy has been ineffective, as described in the above coverage criteria.
- Evidence for gene therapies for hemophilia B is limited to ongoing, small, single -arm, non-randomized, phase 3 trials in patients ≥ 18 years of age, with hemophilia B, having a FIX activity ≤2% of normal, that evaluated the annual bleed rate (ABR) for all bleeds compared to a 6-month run in phase on prophylactic exogenous FIX replacement therapy as their primary endpoint.
    * At the most recent data analysis, both Hemgenix (etranacogene dezaparvovec-drlb) and Beqvez (fidanacogene elaparvovec-dzkt) have reported non-inferiority to the 6-month run of prophylactic exogenous FIX replacement therapy.
- However, the long-term safety, efficacy, and benefit relative to the existing FIX alternatives remains unclear as:
    * The trials were without an active comparator.
    * The trials did not optimize prophylaxis with exogenous factor IX products during the run-in period.
    * There is significant intra-patient variability in terms of FIX therapy response.
    * Due to a limited trial size and short duration, the durability of gene therapies for hemophilia B is unknown.
- Although the phase 3 trial for Beqvez (fidanacogene elaparvovec-dzkt) excluded all patients with anti-AAVRh74 antibodies, Hemgenix (etranacogene dezaparvovec-drlb) was studied in patients with anti-AAV5 antibodies, with no significant difference in efficacy with anti-AAV5 antibody titers up to 679. However, the efficacy in patients with anti-AAV5 titers above 679 is unknown.
- Gene therapies for hemophilia B have not been studied in subjects with a history of FIX inhibitors or in patients less than 18 years of age, therefore use in these settings is considered investigational.
- Current standard of care for long-term management of hemophilia B is routine prophylactic exogenous FIX replacement therapy, with decades of clinical safety and efficacy experience for reduction of bleeding and improvement in quality of life (QOL). Treatment is highly individualized and differs by region and provider preference. The optimal treatment regimen is not known at this time. However, exogenous FIX

replacement therapies have a high clinical burden due to life-long use.

- Additional evidence is needed to assess the long-term safety and efficacy of gene therapies for hemophilia B, including impact on long-term complications, durability, and benefit over existing options in patients that are currently stable on prophylactic exogenous factor IX therapy. Therefore, the use of Hemgenix (etranacogene dezaparvovec-drlb) is considered 'not medically necessary' for the treatment of hemophilia B in patients that are stable on their current prophylactic exogenous factor IX therapy regimen.
- Gene therapies for hemophilia B may be covered for up to one dose per lifetime. There is no data on the safety or efficacy of repeated doses.

Clinical Efficacy [1-3]

Hemgenix (etranacogene dezaparvovec-drlb) for hemophilia B.

- The available evidence for Hemgenix (etranacogene dezaparvovec-drlb) is limited to two ongoing, open-label trials (AMT-061 and HOPE-B) in patients with moderately severe or severe hemophilia B (baseline FIX level ≤2 IU/dL).
    * All patients were at least 18 years of age, on prophylactic exogenous FIX therapy, no history of FIX inhibitors, and no existing liver issues.
    * All patients received a single infusion of Hemgenix (etranacogene dezaparvovec-drlb) at a dose of $2x10^{13}$ vc/kg.
    * The first trial, HOPE-B is an ongoing, multicenter, single arm, phase 3 trial (n=54).
        - All patients were required to participate in a 6-month run-in phase prior to gene therapy administration during which they received prophylactic factor IX. No data is available at this time regarding this run-in period (including impacts on adherence and dosing), which provided a baseline annualized bleeding rate (ABR) for the enrolled subjects.
        - The primary endpoint was ABR at 52 weeks after Hemgenix (etranacogene dezaparvovec-drlb) infusion. The mean ABR at week 52 was 1.51, compared to 4.19 during the run-in phase.
        - A relevant secondary endpoint included the change in FIX activity. At 6-, 12-, and 18-months post-Hemgenix (etranacogene dezaparvovec-drlb) infusion, the FIX activity levels were 39.0 IU/dL, 41.5 IU/dL, and 36.9 IU/dL, respectively.
        - By month 18 post-Hemgenix (etranacogene dezaparvovec-drlb) infusion, 52 patients (96.3%) had discontinued prophylactic factor IX therapy.
    * The second trial, AMT-061, is an unpublished, single arm, phase 2 trial (n=3).
        - The primary endpoint of this trial was FIX activity level.
        - At 12-, 24-, 30-, and 36-months post-Hemgenix (etranacogene dezaparvovec-drlb) infusion, the FIX activity levels were 40.8 IU/dL, 44.2 IU/dL, 50 IU/dL, and 36.9 IU/dL, respectively.

* Despite the reported efficacy in the phase 3 and phase 2 trials above, there are significant limitations in the data which impact the confidence in the data.
    - Small trial size and short duration limit the estimation of clinical effect and the ability to assess the impact on long-term complications as well as long term benefit (durability).
    - Clinical trials did not have an active comparator; therefore, the magnitude of benefit compared to FIX replacement therapies is unknown. Exogenous FIX products have decades of clinical data backing up their safety and efficacy in this population.
    - Significant inter-patient variability in FIX expression was seen during clinical trials. At this time, due to the small sample size of patients treated with Hemgenix (etranacogene dezaparvovec-drlb), no specific variable has been identified that can be used to predict FIX response. Therefore, it is unknown how to determine if a patient will respond to treatment with Hemgenix (etranacogene dezaparvovec-drlb).
    - Subjects with Anti-AAV5 antibodies were studied. No significant difference in FIX expression was observed in subjects with anti-AAV5 antibody titers up to 679. One subject with an anti-AAV5 titer > 3000 did not respond to therapy. There is insufficient data showing that treatment with Hemgenix (etranacogene dezaparvovec-drlb) is effective in patients with anti-AAV5 titers above 679.
    - Hemgenix (etranacogene dezaparvovec-drlb) was not studied in subjects with a history of FIX inhibitors.

<u>Beqvez (fidanacogene elaparvovec-dzkt) for hemophilia B[4-6]</u>

- The safety and efficacy of Beqvez (fidanacogene elaparvovec-dzkt) was established primarily from the ongoing BEGENE-2 trial (n=45), a small, multicenter, single arm open-label, non-inferiority study in patients with moderately severe or severe hemophilia B (baseline FIX level ≤2 IU/dL).
    * Patients were at least 18 years of age, on prophylactic exogenous FIX therapy, with no history of FIX inhibitors, chronic infections, or existing liver disease.
    * Prior to receiving treatment with Beqvez (fidanacogene elaparvovec-dzkt), all patients were in a 6-month run-in phase in which they received prophylactic factor IX therapy. Limited data is available at this time regarding this run-in period (including impacts on adherence and dosing), which provided a baseline annualized bleeding rate (ABR) for the enrolled subjects.
    * After the 6-month run in period, all patients received a single infusion of Beqvez (fidanacogene elaparvovec-dzkt) at a dose of $5x10^{11}$ vg/kg.
    * The primary endpoint was change from baseline in ABR for total bleeds at the end of the efficacy evaluation period (EEP), which was defined as week 12 post Beqvez (fidanacogene elaparvovec-dzkt) infusion up to the most recent data cut off. (median of 1.8 years).

    * The average ABR at the EEP was 2.5, compared to 4.5 during the run-in phase, which met non-inferiority to prophylactic exogenous FIX therapy.
    * Relevant secondary endpoints included FIX activity compared to the run-in period (25% vs ≤2%), and the total number of patients with no bleeds (60% vs 29%).
    * Post-Beqvez (fidanacogene elaparvovec-dzkt) infusion, 38 patients (84%) had discontinued prophylactic factor IX therapy during the EEP.
- Despite the reported efficacy in the phase 3 trial above, there are significant limitations in the data which impact the confidence in the data.
    * Small trial size and short duration limit the estimation of clinical effect, the ability to assess the impact on long-term complications as well as long term benefit (durability).
    * Clinical trials did not have an active comparator; therefore, the magnitude of benefit compared to FIX replacement therapies is unknown. Exogenous FIX products have decades of clinical data backing up their safety and efficacy in this population.
    * Lack of optimization of exogenous FIX prophylactic therapy during the 6-month run in period before treatment with Beqvez (fidanacogene elaparvovec-dzkt) leads to uncertainty.
    * Significant inter-patient variability in FIX expression was seen during the clinical trial. At this time, due to the small sample size of patients treated with Beqvez (fidanacogene elaparvovec-dzkt), no specific variable has been identified that can be used to predict FIX response. Therefore, it is unknown how to determine if a patient will respond to treatment.
    * Beqvez (fidanacogene elaparvovec-dzkt) was not studied in subjects with a history of FIX inhibitors, those <18 years of age, or in patients with anti-AAVRh74 antibodies. Therefore, use in this population is considered investigational.

Guidelines [7]

- Clinical guidelines recommend routine prophylaxis with exogenous FIX replacement therapy as the optimal treatment modality for individuals with severe hemophilia B (FIX <1 IU/dL), with the goal to maintain FIX trough levels above 1 IU/dL. Due to the peaks and troughs seen with exogenous FIX administration, this goal does not apply to gene therapy.
- In 2020, the WFH gene therapy workgroup agreed that the ideal range of FIX expression post-gene therapy should be over 50 IU/dL; however, there was no consensus on the minimum acceptable FIX level. A minimal acceptable level of 10-15% was proposed, but the main concern centered on the 10% minimum factor expression, as this level does not prevent arthropathies.
- Prophylaxis does not reverse established joint damage; however, it reduces ABR, and may slow the progression of joint damage and improve quality of life.
- FIX replacement therapy dosage and dose frequency varies greatly between patients. Dosage is dependent upon the level of severity, the presence of an inhibitor, prescribed

regimen (on-demand, prophylaxis, perioperative), the number of bleeding episodes, individual pharmacokinetics, the products utilized, and the level of physical activity.

Investigational Uses

- Use in pediatrics, patients with inhibitors, or liver dysfunction: At this time, there are no proposed or ongoing trials that will look at the safety or efficacy of gene therapies for hemophilia B in patients less than 18 years of age, with inhibitors to FIX, or liver dysfunction. [8]
- Repeated doses: There is no evidence to establish the safety or efficacy of repeat doses of gene therapies for hemophilia B. If medical necessity criteria are met, only a single dose of gene therapies for hemophilia B will be covered per lifetime. Use of more than one dose is considered 'investigational' and not coverable.

Safety [1 3 4]

- The most common side effects (>10% incidence) experienced during the clinical trials included ALT/AST elevations, headache, influenza-like illness, and infusion related reactions.
- One patient developed hepatocellular carcinoma after treatment with Hemgenix (etranacogene dezaparvovec-drlb). Safety analyses have found that it was not likely linked to therapy based on genetic analysis of the tumor. Off-target insertions in regions not known to be oncogenic were observed. The available data is insufficient to characterize any potential change in cancer risk.
- Due to the small number of patients treated with gene therapies for hemophilia B during clinical trials, additional data is necessary to further define the safety profile.

Appendix 1: Comorbidities which present a significant safety risk
The patient has been appropriately evaluated and ruled out for all of the following: A. Any active infection B. Significant liver dysfunction, defined as any of the following greater than two times the upper limit of normal (ULN): alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), total bilirubin (T bili), and/or alkaline phosphatase (alk phos). C. Advanced liver fibrosis (defined as a Meta-analysis of Histological Data in Viral Hepatitis Stage 3 disease, FibroScan score of ≥9 kPa, or equivalent) D. Documentation of any chronic or active hepatitis B and/or active hepatitis C E. Any active malignancy (except non-melanoma skin cancer)

Codes	Number	Description
HCPCS	J1411	Injection, etranacogene dezaparvovec-drlb (Hemgenix), per therapeutic dose
HCPCS	J3490	Injection, fidanacogene elaparvovec-dzkt (Beqvez), per therapeutic dose

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Revision History

Revision Date	Revision Summary
6/20/2024	• Renamed policy to "Gene therapies for hemophilia B." • Added coverage criteria for use in patients with hemophilia B and significant bleeding sequelae despite use of optimized exogenous factor IX prophylaxis. Hemgenix (etranacogene dezaparvovec-drlb) was previously considered not medically necessary. • Added newly FDA-approved Beqvez (fidanacogene elaparvovec-dzkt) with same intent as above for hemophilia B.
6/15/2023	No changes to criteria with this annual update.
12/9/2022	New policy (effective 1/15/2023). Coverage of Hemgenix (etranacogene dezaparvovec-drlb) is considered not medically necessary for the treatment of adult hemophilia B.

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Medication Policy Manual | **Policy No:** dru736

Topic: Pedmark, sodium thiosulfate | **Date of Origin:** April 15, 2023

Committee Approval Date: March 6, 2025 | **Next Review Date:** 2026

Effective Date: May 1, 2025

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Pedmark (sodium thiosulfate) is an intravenously administered medication that is given to reduce the risk of cisplatin-associated ototoxicity in children who are receiving cisplatin for non-metastatic solid tumors.

PLEASE NOTE: Pedmark (sodium thiosulfate) should not be substituted with other sodium thiosulfate products.

Policy/Criteria

Most contracts require pre-authorization approval of Pedmark (sodium thiosulfate) prior to coverage.

I. Continuation of therapy (COT): Pedmark (sodium thiosulfate) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Pedmark (sodium thiosulfate) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A through E below are met:

A. A diagnosis of a **localized solid tumor**.

AND

B. The disease is not metastatic.

AND

C. Cisplatin will be administered as a treatment.

AND

D. The patient is less than 18 years of age.

AND

E. Pedmark (sodium thiosulfate) will be used to prevent ototoxicity.

III. Pedmark (sodium thiosulfate) is considered investigational when used in adults, and for all other uses and conditions.

IV. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Pedmark (sodium thiosulfate) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Pedmark (sodium thiosulfate) will be authorized in doses up to 20 gm/m^2 in quantities equal to the number of doses of cisplatin that the patient will receive for their treatment course.

C. Authorization may be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

Position Statement

Summary

- Pedmark (sodium thiosulfate) is an intravenously administered medication that is indicated to prevent cisplatin-associated toxicity in pediatric patients who are receiving cisplatin to treat localized, non-metastatic solid tumors.
- The intent of this policy is to allow for coverage of Pedmark (sodium thiosulfate) for pediatric patients with non-metastatic solid tumors who are receiving cisplatin as a treatment in the clinical setting described above, where it has been evaluated for efficacy up to the dose shown to be safe in clinical trials. FDA approval of Pedmark (sodium thiosulfate) was based on two, small, low-quality studies that evaluated hearing loss as an endpoint.
- There is a generic sodium thiosulfate product on the market that received FDA approval as a treatment for cyanide poisoning when used in combination with sodium nitrite. However, this product should not be used in place of Pedmark as the formulations differ. Pedmark (sodium thiosulfate) is the only product that has been studied in pediatric patients to decrease the risk of hearing loss associated with cisplatin.
- The effects of cisplatin-associated ototoxicity are greatest in children as they can lead to impairment in speech and language acquisition, psychosocial and cognitive development, and educational and vocational achievement. Risk factors for developing cisplatin-induced ototoxicity include age < 5 years, cumulative cisplatin dose > 200 mg/m^2 to 400 mg/m^2, extended duration of therapy, and cranial irradiation involving the cochlea.
- Pedmark (sodium thiosulfate) is considered investigational when used in adult patients, and in other clinical settings (e.g., to prevent other cisplatin-associated toxicities) where its safety and effectiveness have not been adequately evaluated.

Pedmark (sodium thiosulfate) is the only guideline-recommended treatment for prevention of cisplatin-based ototoxicity in children. Other therapies have been used off-label for this purpose in the past; however, they are not part of current recommendations.

- Pedmark (sodium thiosulfate) is given six hours after each cisplatin infusion. Because it works via inactivation of platinum compounds in the body, timing of doses is crucial. Dosing should be completed within 10 hours of the next scheduled dose of cisplatin.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Background [1,2]

- Ototoxicity due to cisplatin exposure is common and results from the death of cochlear outer hair cells. It occurs in 60% to 80% of children treated with cisplatin and is generally permanent and progressive.
- The effects of cisplatin-associated ototoxicity are greatest in children as they can lead to impairment in speech and language acquisition, psychosocial and cognitive development, and educational and vocational achievement.
- Risk factors for developing cisplatin-induced ototoxicity include age < 5 years, cumulative cisplatin dose > 200 mg/m^2 to 400 mg/m^2, extended duration of therapy, and cranial irradiation involving the cochlea.

Clinical Efficacy [2,3]

- The efficacy of Pedmark (sodium thiosulfate) was evaluated in two randomized controlled, open-label studies in pediatric patients with localized solid tumors who were receiving cisplatin as a treatment.

    * One study evaluated children with hepatoblastoma while the other included children with other types of solid tumors.
    * Only children with non-metastatic disease were allowed to participate in the studies.
    * The studies compared the children who received Pedmark (sodium thiosulfate) in conjunction with cisplatin therapy with those who did not.
    * The proportion of patients with hearing loss (per audiometry) was measured as the primary endpoint. Overall survival was measured as a secondary endpoint because Pedmark (sodium thiosulfate) has the potential to interfere with the efficacy of cisplatin. (Investigators wanted to demonstrate there was a potential benefit but that it was not compromising the efficacy of the chemotherapy).
    * There was a statistically significant decrease in the number of children experiencing hearing loss at the end of therapy in the Pedmark (sodium thiosulfate) treatment arm relative to the control arm in both studies.
    * One study also evaluated hearing loss one year after completion of Pedmark (sodium thiosulfate) as an exploratory endpoint. Statistically fewer children in the Pedmark (sodium thiosulfate) treatment arm experienced hearing loss at one year relative to the control arm.
    * No statistically significant differences in overall survival were noted between the Pedmark (sodium thiosulfate) and control groups; however, it cannot be ruled out that the ability to detect a difference may have been impaired by the small numbers of children enrolled in each study.
- Current evidence for Pedmark (sodium thiosulfate) as a therapy to prevent cisplatin-associated hearing loss is based on studies of a relatively short duration. Studies of longer duration are needed to confirm whether this therapy contributes to long-term outcomes.

Guidelines [1]

- The Lancet Health Clinical Practice Guideline on Prevention of Cisplatin-Induced Ototoxicity in Children and Adolescents with Cancer recommends Pedmark (sodium thiosulfate) to prevent cisplatin-induced ototoxicity in patients with non-metastatic hepatoblastoma (strong recommendation) and in other non-metastatic cancers (weak recommendation). No other treatments are recommended for this use.

Investigational Uses [4]

- Sodium thiosulfate is used in combination with sodium nitrate as part of a protocol to treat cyanide poisoning. There is a specific formulation of sodium thiosulfate (generic) specifically approved for this use. The use of the Pedmark formulation for the treatment of cyanide poisoning is considered investigational.
- Based its mechanism of action, there is interest in using Pedmark (sodium thiosulfate) to prevent other cisplatin-associated toxicities (e.g., prevent renal toxicity). The safety and effectiveness of Pedmark (sodium thiosulfate) in these other settings have not been established. Use other than prevention of cisplatin-associated ototoxicity in pediatric patients is considered investigational.

Safety [5]

- Electrolyte disturbances are the most common adverse effects associated with Pedmark (sodium thiosulfate).
- Gastrointestinal effects were also observed in patients who received Pedmark (sodium thiosulfate); however, they are also common with the background cisplatin-based regimens that were given during the studies.

Dosing [5]

- Pedmark (sodium thiosulfate) is administered intravenously over 15 minutes.
- The timing of Pedmark (sodium thiosulfate) dosing is critical. The infusion must be given 6 hours after the completion of the cisplatin infusion but at least 10 hours prior to the next cisplatin infusion.
- Dosing is based on patient weight. Consult package labelling for appropriate dosing.

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Revision History

Revision Date	Revision Summary
3/6/2025	No criteria changes with this annual review.
3/21/2024	No criteria changes with this annual review.
3/16/2023	New Policy (effective 4/15/2023). • Limits coverage of Pedmark (sodium thiosulfate) to pediatric patients (< 18 years of age) who are receiving cisplatin to treat localized, non-metastatic solid tumors. • All other uses are considered investigational.

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Medication Policy Manual **Policy No:** dru740

Topic: Monoclonal antibodies for Alzheimer's disease **Date of Origin:** April 15, 2023

- Aduhelm, aducanumab
- Kisunla (donanemab)
- Leqembi, lecanemab

Committee Approval Date: September 19, 2024 **Next Review Date:** 2025

Effective Date: December 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Medications included in this policy are monoclonal antibodies used for Alzheimer's disease (AD). A clinical benefit, such as slowing of disease progression, of these monoclonal antibodies for Alzheimer's disease has yet to be established.

Policy/Criteria

Most contracts require pre-authorization approval of monoclonal antibodies for Alzheimer's disease (as listed in Table 1) prior to coverage.

I. Continuation of therapy (COT): Monoclonal antibodies for Alzheimer's disease (as listed in Table 1) may be considered medically necessary for COT when full policy criteria below are met, including quantity limit.

Please note: *Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Monoclonal antibodies for Alzheimer's disease (as listed in *Table 1*) are considered investigational for all conditions, including Alzheimer's disease.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers monoclonal antibodies for Alzheimer's disease (as listed in *Table 1*) coverable under the medical benefit (as a provider-administered medication).

B. Although the use of monoclonal antibodies for Alzheimer's disease (as listed in *Table 1*) is considered "investigational," if pre-authorization is approved, monoclonal antibodies for Alzheimer's disease (as listed in *Table 1*) will be authorized as follows:

TABLE 1.

Product	Quantity Limit
Aduhelm (aducanumab)	Doses up to 10 mg/kg every 4 weeks.
Kisunla (donanemab)	Doses up to 1400 mg every 4 weeks.
Leqembi (lecanemab)	Doses up to 10 mg per kg every 2 weeks.

C. Authorization **shall** be reviewed at least every six months for documented benefit. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met. Specifically, documentation that the medication is providing clinical benefit, including disease stability or improvement, and lack of disease progression.

Position Statement

Summary

- Monoclonal antibodies for Alzheimer's disease (AD), Aduhelm (aducanumab), Kisunla (donanemab) and Leqembi (lecanemab), are intravenous therapies indicated for the treatment of AD.

- A clinical benefit (e.g. prolongation of independence, improved quality of life, prevention of disease progression and disability) with monoclonal antibodies for AD has not been established. [1 2]
    * The results of two nearly identical unpublished studies (EMERGE and ENGAGE) [1 3] of Aduhelm (aducanumab) had inconsistent clinical benefit after 18 months of treatment. Of the two trials, one demonstrated cognitive and functional improvements based on clinical scores in a subgroup who received high dose aducanumab while no endpoint was met in a second study regardless of dose.
    * In the TRAILBLAZER-ALZ2 trial, treatment with Kisunla (donanemab) resulted in cognitive and functional improvements after 18 months of treatment. However, the clinical meaningfulness of the improvement is unclear as the changes did not meet the defined minimal clinically important difference. [4]
    * Both studies (Study 201 and CLARITY AD) of Leqembi (lecanemab) demonstrated cognitive and functional improvements based on clinical scores, however in Study 201 those scores did not meet the threshold of prespecified success and in CLARITY AD the clinical relevance of the improvement is unclear and did not meet the defined minimal clinically important difference. [2 5-7]
    * Aduhelm (aducanumab), Kisunla (donanemab) and Leqembi (lecanemab) demonstrated improvements in amyloid beta imaging; however, the reduction of beta-amyloid plaque is a surrogate endpoint whose causal link to clinical benefit for patients with AD has yet to be established. [2]
    * Given the lack of overall clinical benefit and potential for harms, the use of monoclonal antibodies for AD is considered investigational.
- Of note: The manufacturer announced discontinuation of Aduhelm (aducanumab) in late 2024.
- Treatment of AD is largely supportive and may include the avoidance of poly-pharmacy as well as treatment of comorbid conditions. Currently available pharmacological therapy focuses on symptom management but does not modify disease course. [8]

Clinical Efficacy

Aduhelm (aducanumab) for Alzheimer's disease

- The results of two nearly identical studies did not have consistent clinical benefit after 18 months of treatment. The FDA standard is typically two demonstrative clinical trials with positive data on patient reported outcomes/symptoms.
- The evidence regarding the effect of Aduhelm (aducanumab) is based on the change from baseline on the CDR-Sum of Boxes is inconclusive. The (CDR-SB) is an extensive cognitive and functional assessment tool used primarily in clinical trials. Higher scores suggest greater disease severity; a minimal clinically significant difference (MCID) is estimated to be 1-2 points. [9]

- Patients in the pivotal trials had prodromal or mild AD along with confirmed amyloid pathology [positive amyloid positron emission tomography (PET) scan]. All patients in the trials had either mild cognitive impairment associated with AD or mild AD; patients with more severe disease were not studied.
    * EMERGE: A statistically significant improvement in CDR-SB was observed in the high-dose aducanumab arm (difference vs. placebo -0.39 [95% CI -0.69 to -0.09]) but not the low-dose arm. Although the results were statistically significant in the high-dose arm, the change in CDR-SB was less than the 1-2 point change that has been suggested as the MCID.
    * ENGAGE: Neither low dose or high dose had any statistically significant improvement vs placebo in CDR-SB or any secondary efficacy endpoints.
- Both studies demonstrated significant improvements in amyloid plaques based on PET imaging; however, the effect of amyloid beta on clinical outcomes has not yet been established. There have been 16 trials of other drugs in which the treatment arm did worse than placebo despite reduction of amyloid, albeit typically in a population with more severe disease. [2]
- Although the existing evidence is promising, an additional confirmatory trial is needed to establish the safety and efficacy of Aduhelm (aducanumab) in AD. Aduhelm (aducanumab) has not yet proven to improve clinically relevant outcomes such as quality of life, prolongation of independent functioning, or prevention of disease progression and disability, or mortality.
- The FDA advisory committee as well as the Institute for Clinical and Economic Review (ICER) openly advised against approval of Aduhelm (aducanumab). [10 11] Prior to approval, the American Academy of Neurology (AAN) advised against a broad label approval and that further characterization of patients who would benefit most is warranted. [8]
- At this time, there is not enough data available to determine that the benefits of Aduhelm (aducanumab) use would outweigh the risks or provide any meaningful benefit in the AD population. Aduhelm (aducanumab) has uncertain benefit in the face of known harms.

Kisunla (donanemab) for Alzheimer's disease

- The efficacy of Kisunla (donanemab) was evaluated in a single phase 3, double-blind, placebo-controlled trial (TRAILBLAZER-ALZ2, N=1736) in patients with AD with mild cognitive impairment or mild dementia. [4]
    * Results of the trial showed that patients treated with Kisunla (donanemab) achieved greater improvements compared to placebo based on the integrated Alzheimer's Disease Rating Scale (iADRS).
    * The iADRS is a cognitive and functional assessment scale that combines components of two other AD scales commonly used in clinical trials. Scores in the iADRS can range from 0 to 144 with lower scores indicating greater disease severity.

    * The minimal clinically important difference (MCID) for a score is 5 points in AD with mild cognitive impairment and 9 points in AD with mild dementia. After 18 months of treatment, the difference in the iADRS scores between Kisunla (donanemab) and placebo was 2.9, which did not reach the threshold for clinically meaningful change for cognition or function.[4]

- Although the existing evidence is promising, additional confirmatory trials are needed to establish the safety and efficacy of Kisunla (donanemab) in AD. Based on the results of the TRAILBLAZER trial, there is not enough evidence that any potential benefit of treatment with Kisunla (donanemab) outweighs the harms associated with treatment. Kisunla (donanemab has not yet proven to improve clinically relevant outcomes such as prolongation of independent functioning nor has it proven prevention of disease progression and disability, or mortality.

Leqembi (lecanemab) for Alzheimer's disease

- The FDA accelerated approval of Leqembi (lecanemab) was based on a single phase 2b, double-blind, placebo-controlled, dose finding trial (Study 201, N=856). The FDA standard is typically two demonstrative clinical trials with positive data on patient reported outcomes/symptoms. [5 7 12] A phase 3, global, multicenter, randomized, double-blind placebo-controlled confirmatory trial (CLARITY AD, N=1795) has since been published, submitted to FDA, and received full approval. [6]
- The evidence regarding the effect of Leqembi (lecanemab) based on the change from baseline on the CDR-Sum of Boxes is inconclusive. The (CDR-SB) is an extensive cognitive and functional assessment tool used primarily in clinical trials. Higher scores suggest greater disease severity; MCID is estimated to be 1-2 points. The clinical relevance of the effect that Leqembi (lecanemab) showed (slowing of CRD-SB by 0.45 compared to placebo at 18 months) is unclear at this time as it falls below the MCID. [2]
- Patients in both pivotal trials had either mild cognitive impairment associated with AD or mild dementia due to AD. Patients with more severe disease were not studied. Confirmation of amyloid pathology [positive amyloid positron emission tomography (PET) scan or via cerebrospinal fluid (CSF)] was also required. [6 12]
    * Study 201: An improvement in the primary endpoint of the change in baseline on a weighted composite score from Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB), the Mini-Mental State Examination (MMSE) and the AD assessment scale-Cognitive 14 Subscale (ADAS-Cog 14) was shown at week 53 (64% likelihood of a 25% or greater slowing of progression) with Leqembi (lecanemab) when compared to placebo. However, the results did NOT meet prespecified success criterion of 80%. [5]
    * CLARITY AD: A statistically significant improvement in the primary endpoint of the change from baseline of CDR-SB at month 18 was observed in the Leqembi (lecanemab) arm (difference vs. placebo -0.45 [95% CI -0.67 to -0.23, p-value of 0.00005], which represents a 27% reduction in progression). Although the results were statistically significant, the change in CDR-SB was less than the 1–2-point change that has been suggested as the minimal clinically important difference (MCID). [6]

- Both studies demonstrated significant improvements in amyloid plaques based on PET imaging; however, the effect of amyloid beta on clinical outcomes has not yet been established. There have been at least previous 16 trials of other drugs in which the treatment arm did worse than placebo despite reduction of amyloid, albeit typically in a population with more severe disease. [2]
- Although the existing evidence is promising, additional confirmatory trials are needed to establish the safety and efficacy of Leqembi (lecanemab) in AD. Lecanemab (lecanemab) has not yet proven to improve clinically relevant outcomes such as prolongation of independent functioning nor has it proven prevention of disease progression and disability, or mortality. [13]
- At this time, even with the recent phase 3 trial outcomes noted above resulting in full FDA approval, there is not enough data available to determine that the benefits of Leqembi (lecanemab) use would outweigh the risks or provide any meaningful benefit in the AD population. Leqembi (lecanemab) has uncertain benefit in the face of known harms.

Safety

- 40% of patients on the high-dose Aduhelm (aducanumab) had amyloid related imaging abnormalities (ARIA) which may be linked to brain bleeds/swelling. [1]
- 36.8% of patients treated with Kisunla (donanemab) experienced ARIA reactions compared to 14.9% of patients treated with placebo. [14]
- 21.5% of patients on Leqembi (lecanemab) had ARIA reactions compared to only 9.5% in placebo. [7]
- Labeling for monoclonal antibodies for AD carry warnings for ARIA as well as require periodic brain magnetic resonance imaging (MRI) to monitor for ARIA.

Cross References
BlueCross BlueShield Association Medical Policy, 5.01.38 - Aducanumab for Alzheimer Disease [November 2022]

Codes	**Number**	**Description**
HCPCS	J0172	Injection, aducanumab-avwa (Aduhelm), 2 mg
HCPCS	J0175	Injection, donanemab (Kisunla), 17.5 mg
HCPCS	J0174	Injection, lecanemab-irmb (Leqembi), 1 mg

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14. Kisunla (donanemab) [Prescribing Information]. Indianopolis, IN: Eli Lilly; July 2024.

Revision History

Revision Date	Revision Summary
9/19/2024	Added newly FDA-approved Kisunla (donanemab) to policy.
12/7/2023	No criteria changes with this annual review.
9/14/2023	Updated position statement to reflect recent Leqembi (lecanemab) full FDA approval. Leqembi (lecanemab) has now received full approval based upon the results of the CLARITY AD trial. No change to criteria.
3/16/2023	New combination policy (effective 4/15/2023) Combined newly FDA-approved drug Leqembi (lecanemab) with previously medication policy: dru670 Aduhelm (aducanumab), into a new policy, monoclonal antibodies for Alzheimer's disease with no change to intent.

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Medication Policy Manual | **Policy No:** dru743

Topic: Adstiladrin, nadofaragene firadenovec-vncg | **Date of Origin:** July 15, 2023

Committee Approval Date: December 7, 2023 | **Next Review Date:** 2024

Effective Date: March 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Adstiladrin (nadofaragene firadenovec-vncg) is instilled into the bladder (intravesical administration) as a treatment for high-risk, non-muscle invasive bladder cancer (NMIBC) that is unresponsive to Bacillus Calmette-Guérin (BCG). It is administered by a trained healthcare provider.

Policy/Criteria

Most contracts require pre-authorization approval of Adstiladrin (nadofaragene firadenovec-vncg) prior to coverage.

I. Continuation of therapy (COT): Adstiladrin (nadofaragene firadenovec-vncg) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Adstiladrin (nadofaragene firadenovec-vncg) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A through E below are met:

A. A diagnosis of **non-muscle invasive bladder cancer (NMIBC)** with carcinoma *in situ* (CIS) either with or without papillary tumors.

AND

B. The tumor is Bacillus Calmette-Guérin (BCG)-unresponsive as defined by the following (1 or 2):

1. Persistent or recurrent CIS alone after adequate BCG therapy (refer to *Appendix 1*).

OR

2. Recurrent Ta/T1 disease within 12 months of BCG therapy.

AND

C. The patient is ineligible for or has elected not to undergo cystectomy (removal of the bladder).

AND

D. Treatment with Keytruda (pembrolizumab) was not tolerated or is contraindicated.

AND

E. Adstiladrin (nadofaragene firadenovec-vncg) will be used as monotherapy.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy services considers Adstiladrin (nadofaragene firadenovec-vncg) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Adstiladrin (nadofaragene firadenovec-vncg) will be authorized in a dose of 75 ml for up to two instillations per six months.

C. Authorization **shall** be reviewed at least every six months for documented benefit. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

IV. Adstiladrin (nadofaragene firadenovec-vncg) is considered investigational when used for all other conditions.

Position Statement

Summary

- Adstiladrin (nadofaragene firadenovec-vncg) is a gene therapy designed to introduce a human interferon alfa-2b gene into bladder cancer cells. Once inserted, this gene causes the cancer cells to produce interferon which results in the cancer cells' destruction.
- Adstiladrin (nadofaragene firadenovec-vncg) is given via intravesical administration (instilled into the bladder). It is indicated as a monotherapy for the treatment of adult patients with high-risk Bacillus Calmette-Guérin (BCG)-unresponsive non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors.
- The intent of this policy is to allow for coverage of Adstiladrin (nadofaragene firadenovec-vncg) where it has been shown to be effective, up to the dose shown to be safe and effective in clinical trials, as detailed in the coverage criteria.
- Adstiladrin (nadofaragene firadenovec-vncg) received FDA approval based on a low-quality, single-arm study in patients with high-risk BCG-unresponsive NMIBC with CIS with or without papillary tumors. The study evaluated complete response as the primary endpoint.

- Tumor response, a surrogate endpoint, has not been shown to accurately predict improvement in any clinically relevant outcome. It is not known if responses will be durable or will translate into improved overall survival (OS), the clinical outcome of interest.
- Keytruda (pembrolizumab) has also been evaluated in a similar population of patients. The study design, quality, size, and results were generally similar to the Adstiladrin (nadofaragene firadenovec-vncg) study. Keytruda (pembrolizumab) currently provides a better value over Adstiladrin (nadofaragene firadenovec-vncg).
- Adstiladrin (nadofaragene firadenovec-vncg) is relatively well tolerated. There may be instillation site discharge, bladder spasm, urination urgency, and dysuria associated with the intravesical administration. Other side effects may include fatigue, fever, and chills.
- The National Comprehensive Cancer Network (NCCN) guideline lists cystectomy (bladder removal), Keytruda (pembrolizumab), Adstiladrin (nadofaragene firadenovec-vncg), and intravesical chemotherapy as potential therapies for high-grade, BCG-unresponsive NMIBC.
- Adstiladrin (nadofaragene firadenovec-vncg) is administered via intravesical instillation by a trained healthcare provider every three months. The solution must be retained in the bladder for an hour after instillation. Because it contains a viral vector, voided urine should be disinfected with a virucidal agent for 30 minutes before disposal.
- The safety and effectiveness of Adstiladrin (nadofaragene firadenovec-vncg) have not been adequately studied in other disease settings. Therefore, use in settings other than that which is described above are considered investigational.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Background *[1,2]*

- Non-muscle invasive bladder cancer (NMIBC) may affect the bladder urothelium, or the bladder epithelium and subepithelial connective tissue immediately underlying the urothelium but has not yet invaded the muscle layer of the bladder.
- Management of NMIBC is directed at reducing disease recurrence and preventing disease from progressing to more advanced stages.
- Bacillus Calmette-Guérin (BCG) is the main therapy used in the management of NMIBC. It is an immunotherapy that works by stimulating the immune system within the bladder which leads to the destruction of cancer cells. It is typically given after transurethral resection of the bladder (TURBT).

Clinical Efficacy

- The efficacy of intravesical Adstiladrin (nadofaragene firadenovec-vncg) monotherapy was evaluated in a small (N=98), low quality, single-arm, open-label study in adults with NMIBC who had become unresponsive to treatment with BCG. Tumor response was evaluated as the primary surrogate endpoint. [1,3]
    * Seventy-six percent of the population had carcinoma *in situ* (CIS) only, 19% had CIS with Ta tumors, and 5% had CIS with T1 tumors. (Refer to *Appendix 2* for staging definitions.)
    * Fifty-three percent were refractory to BCG therapy and 47% had relapsed disease after adequate BCG therapy.
    * Patients with upper tract urothelial carcinoma (UC) or UC within the prostatic urethra were excluded from participating in the study.
    * Complete response was reported in 51% of the study population with a median duration of response of 9.7 months. There is no comparative or outcomes data. It is also not known if this therapy limits future metastasis of bladder cancer.
- Keytruda (pembrolizumab) was evaluated in a small (N=96), low quality, single-arm, open-label study (KEYNOTE-057) in a similar population. Complete response was reported in 41% of subjects with a median duration of response of 16.2 months. [4,5]

Guidelines *[2]*

- The National Comprehensive Cancer Network (NCCN) urothelial carcinoma guideline recommends the following for high-grade NMIBC that is not responsive to or recurs after BCG: Cystectomy (removal of the bladder), Keytruda (pembrolizumab), Adstiladrin (nadofaragene firadenovec-vncg), or intravesical chemotherapy.
- The guideline notes that both Keytruda (pembrolizumab) and Adstiladrin (nadofaragene firadenovec-vncg) are appropriate for CIS with or without papillary tumors.

Investigational Uses *[6]*

- There is an ongoing study of intrapleural Adstiladrin (nadofaragene firadenovec-vncg) in malignant pleural mesothelioma when given in combination with chemotherapy. There are currently no results available from this trial.
- There are no published clinical studies evaluating Adstiladrin (nadofaragene firadenovec-vncg) in conditions other than NMIBC.

Safety [7]

- Adstiladrin (nadofaragene firadenovec-vncg) was generally well tolerated in clinical trials.
- Because Adstiladrin (nadofaragene firadenovec-vncg) uses a viral vector, spills should be treated with a virucidal agent for 30 minutes. Additionally, voided urine should be disinfected for 30 minutes with an equal volume of virucidal agent before flushing of the toilet.

Dosing [7]

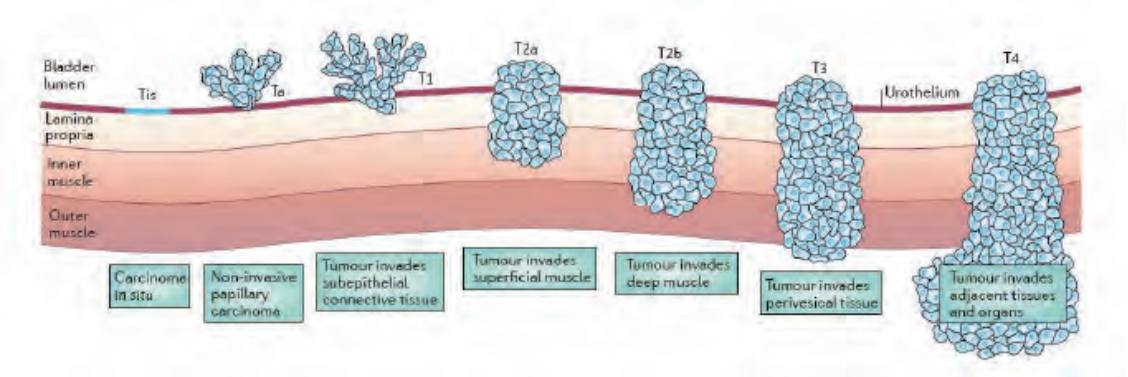
- Adstiladrin (nadofaragene firadenovec-vncg) is given via intravesical instillation once every three months by a trained provider (most likely a urologist). The suspension must be maintained in the bladder for one hour after instillation.
- Refer to the Adstiladrin (nadofaragene firadenovec-vncg) prescribing information for specific information regarding dose, premedication, dosing interval, and administration.

Appendix 1: Standard Definition of BCG Failure [1]
BCG-unresponsive CIS: Persistent or recurrent CIS alone or with recurrent Ta/T1 disease within 12 months of adequate BCG therapy. Adequate BCG therapy is defined as at least five of six doses of an initial induction course plus at least two or three doses of maintenance BCG, or at least five of six doses of initial induction course plus at least two of six doses of a second induction course.

Appendix 2: AJCC Staging of NMIBC [2] (refer to Figure 1 below)
T = Primary tumor
Ta = Noninvasive papillary tumor
Tis = Urothelial carcinoma *in situ* (CIS; 'flat tumor')
T1 = Tumor invades lamina propria (subepithelial connective tissue)

AJCC = American Joint Committee on Cancer

Figure 1: Bladder Cancer Classification [8]



Cross References
Keytruda, pembrolizumab, Medication Policy Manual, Policy No. dru367

Codes	Number	Description
HCPCS	J9029	Injection, nadofaragene firadenovec-vncg (Adstiladrin).

References

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Revision History

Revision Date	Revision Summary
12/7/2023	No criteria changes with this annual review.
6/15/2023	New policy (effective 7/15/2023) limits coverage of Adstiladrin (nadofaragene firadenovec-vncg) as monotherapy for BCG-unresponsive, high-grade NMIBC when patients are not eligible for or elect not to undergo cystectomy and are not a candidate for Keytruda (pembrolizumab).

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Medication Policy Manual | **Policy No:** dru745

Topic: Lunsumio, mosunetuzumab-axgb | **Date of Origin:** July 15, 2023

Committee Approval Date: March 21, 2024 | **Next Review Date:** 2025

Effective Date: June 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Lunsumio (mosunetuzumab-axgb) is an intravenously administered immunotherapy used in the management of follicular lymphoma (FL). It helps T-cells recognize and destroy lymphoma cells that express the CD20 antigen.

Policy/Criteria

Most contracts require pre-authorization approval of Lunsumio (mosunetuzumab-axgb) prior to coverage.

I. Continuation of therapy (COT): Lunsumio (mosunetuzumab-axgb) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Lunsumio (mosunetuzumab-axgb) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A, B, C, and D below are met:

A. A diagnosis of **follicular lymphoma (FL)**, relapsed or refractory.

AND

B. The FL is Grade 1-2, or 3a.

AND

C. The FL relapsed after or was refractory to at least two prior systemic therapies which must have included each of the following (1 and 2):

1. An alkylating agent (see *Appendix A*).

AND

2. An anti-CD20-directed monoclonal antibody (see *Appendix B*).

AND

D. Lunsumio (mosunetuzumab-axgb) will be given as monotherapy.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy services considers Lunsumio (mosunetuzumab-axgb) coverable only under the medical benefit (as a provider-administered medication).

B. ***Initial authorization:*** When pre-authorization is approved, Lunsumio (mosunetuzumab-axgb) will be authorized for up to eight, 21-day cycles (a quantity of ten infusions including the two initial test doses administered in the first cycle).

C. ***Additional authorization:***

1. *For complete response:* If a complete response is achieved after the initial eight cycles of Lunsumio (mosunetuzumab-axgb), no additional cycles will be authorized.

2. *For partial response or stable disease:* If a partial response or stable disease is achieved after the initial eight cycles of Lunsumio (mosunetuzumab-axgb), up to nine additional 21-day cycles may be authorized. No additional Lunsumio (mosunetuzumab-axgb) will be authorized (17 cycles in total).

IV. Lunsumio (mosunetuzumab-axgb) is considered investigational when used for Grade 3b FL, and for all other conditions.

Position Statement

Summary

- Lunsumio (mosunetuzumab-axgb) is an intravenously administered bispecific T-cell engager that binds to the CD3 receptor on T-cells and the CD20 antigen expressed on the surface of lymphoma cells thus initiating an immune response. It is indicated as a monotherapy for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after two or more lines of systemic therapy.
- The intent of this policy is to allow for coverage of Lunsumio (mosunetuzumab-axgb) as a monotherapy for relapsed or refractory FL after at least two prior lines of systemic therapy, including an alkylating agent and an anti-CD20-directed monoclonal antibody.
- Lunsumio (mosunetuzumab-axgb) received FDA *accelerated* approval based on a single-arm study in patients with Grades 1 to 3a FL who had relapse after or failed to respond to at least two prior systemic therapies. All patients had prior therapy with an alkylating agent and an anti-CD20-directed monoclonal antibody. The study evaluated tumor response as the primary endpoint.
- Tumor response, a surrogate endpoint, has not been shown to accurately predict improvement in any clinically relevant outcome. Though tumor responses in the study were quite high, it is not yet known if they will be durable and will translate into improved overall survival, the clinical outcome of interest.
- As observed with chimeric antigen receptor T-cell therapies, the strong T-cell response initiated with Lunsumio (mosunetuzumab-axgb) can lead to serious harms including cytokine release syndrome (CRS) and neurological toxicity. It should only be administered by qualified healthcare professionals with experience and appropriate medical support to manage these toxicities.
- The National Comprehensive Cancer Network (NCCN) guideline includes Lunsumio (mosunetuzumab-axgb) among its recommendations for Grade 1-2 FL. The guideline notes that the treatment of Grade 3a FL is individualized, and that Grade 3b FL (transformed FL) should be treated as diffuse large B-cell lymphoma (DLBCL).
- Lunsumio (mosunetuzumab-axgb) is administered intravenously every 21 days over 2 hours; however, it must be initiated with small test doses administered over 4 hours to minimize the risk of severe CRS. Lunsumio (mosunetuzumab-axgb) is given for an initial 8 cycles after which response is evaluated. For patients who do not achieve a complete response with the initial 8 cycles (partial response or stable disease) an additional 9 cycles may be administered (up to 17 cycles total).
- The safety and effectiveness of Lunsumio (mosunetuzumab-axgb) have not been adequately studied in other disease settings. Therefore, use in settings other than that which is described above are considered investigational.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Background [1]

- Follicular lymphoma (FL) is the second most common non-Hodgkin lymphoma (NHL).
- The World Health Organization (WHO) classifies FL using several Grades (FL1-2, FL3A, FL3B) based on the number of centroblasts that are present to stratify patients based on expected outcomes. Grade 3B FL is also known as 'transformed FL' and is generally treated using therapy pathways for diffuse large B-cell lymphoma (DLBCL).

Clinical Efficacy [2,3]

- The efficacy of Lunsumio (mosunetuzumab-axgb) was evaluated in a single-arm, open-label study in adults with Grade 1 to 3A, relapsed or refractory FL that evaluated tumor response as the primary endpoint.
    * Patients in the study relapsed after or failed to respond to at least two prior systemic therapies (median of 3). All patients had a prior alkylating agent and a prior anti-CD20-directed monoclonal antibody. Three percent of patients had a prior chimeric antigen receptor (CAR) T-cell therapy for their FL.
    * Patients with prior allogeneic stem cell transplant (SCT) were excluded from participating in the study due to the high likelihood of severe immune reactions; however, 21% of the population had a prior autologous SCT.
    * The objective response rate (ORR) was 80% with 60% being complete responses. The median duration of response was 22.8 months.
- Though the reported ORRs were very high in this study, it is not yet known how durable the responses will be, or whether Lunsumio (mosunetuzumab-axgb) will ultimately

improve overall survival, the clinical outcome of interest. Lunsumio (mosunetuzumab-axgb) has not been directly compared with any other therapy, including CAR T-cell therapies which also are associated with high ORRs.

Guidelines [1]

- The National Comprehensive Cancer Network (NCCN) B-cell lymphomas guideline lists Lunsumio (mosunetuzumab-axgb) among potential systemic therapy options for relapsed or refractory FL (Grade 1-2) in the third- and subsequent-line treatment setting.
- The NCCN guideline notes that Grade 3B FL should be treated using the DLBCL pathway.

Investigational Uses [4]

- Lunsumio (mosunetuzumab-axgb) is only indicated as a monotherapy. Future studies are planned which combine it with other medications such as lenalidomide; however, the safety and efficacy of these combinations is not yet established.
- Based on its mechanism of action there may be interest in using Lunsumio (mosunetuzumab-axgb) in other B-cell malignancies; however, the safety and efficacy in diseases other than relapsed or refractory FL have not been established.

Safety [5]

- There is a boxed warning for Lunsumio (mosunetuzumab-axgb) indicating that it has the potential to cause severe and life-threatening cytokine release syndrome (CRS). It may also cause severe neurologic toxicity. Like CAR T-cell therapies it should only be administered by qualified healthcare professionals with experience and appropriate medical support to manage these toxicities.
- In the clinical study Lunsumio (mosunetuzumab-axgb) was also associated with cytopenias, infections, fatigue, and electrolyte disturbances.

Dosing [5]

- Lunsumio (mosunetuzumab-axgb) is given on Day 1 of each 21-day cycle. However, in the first cycle, two small test doses are given on Days 1 and 8 to make sure the patient tolerates the medication before proceeding to the full regimen.
- Lunsumio (mosunetuzumab-axgb) is given for an initial 8 cycles at which point response to therapy is assessed. If the patient has a complete response to therapy, no additional medication is given. If there is a partial response or stable disease, up to nine additional cycles of Lunsumio (mosunetuzumab-axgb) may be administered (total of 17 cycles).
- Refer to the Lunsumio (mosunetuzumab-axgb) prescribing information for the specific information regarding dose, dosing intervals, and infusion times.

Appendix A: Alkylating Agents Used in the Treatment of Follicular Lymphoma (FL)
Bendamustine (Treanda)
Chlorambucil (Leukeran)
Cyclophosphamide (Cytoxan)

Appendix B: Anti-CD20-Directed Monoclonal Antibodies Used in the Treatment of FL
Obinutuzumab (Gazyva)
Rituximab (Rituxan)

Cross References
PI3K Inhibitors, Medication Policy Manual Policy No. dru706
Chimeric Antigen Receptor (CAR) T-cell Therapies, Medication Policy Manual Policy No. dru523
Tazverik, tazemetostat, Medication Policy Manual Policy No. dru627

Codes	Number	Description
HCPCS	J9350	Injection, mosunetuzumab-axgb, 1 mg

References

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Revision History

Revision Date	Revision Summary
3/21/2024	No criteria changes with this annual review.
6/15/2023	New policy (effective 7/15/2023) limits coverage of Lunsumio (mosunetuzumab-axgb) as monotherapy for relapsed or refractory, Grades 1-2 or 3a follicular lymphoma after at least two prior systemic therapies which must have included an alkylating agent and an anti-CD20-directed monoclonal antibody.

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Medication Policy Manual | **Policy No:** dru751

Topic: Zynyz, retifanlimab-dlwr | **Date of Origin:** July 15, 2023

Committee Approval Date: September 19, 2024 | **Next Review Date:** 2025

Effective Date: January 1, 2025

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Zynyz (retifanlimab-dlwr) is an intravenously administered immunotherapy used in the management of a specific type of skin cancer. It belongs to a class of medications called programmed death receptor-1 (PD-1) blocking antibodies.

Policy/Criteria

Most contracts require pre-authorization approval of Zynyz (retifanlimab-dlwr) prior to coverage.

I. Continuation of therapy (COT): Zynyz (retifanlimab-dlwr) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Zynyz (retifanlimab-dlwr) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A, B, C, and D below are met:

A. A diagnosis of **Merkel cell carcinoma** (MCC), recurrent locally advanced or metastatic.

AND

B. No prior systemic therapy (chemotherapy or immunotherapy) was used in the advanced disease setting.

AND

C. Zynyz (retifanlimab-dlwr) will be used as monotherapy.

AND

D. No prior programmed death receptor-1 (PD-1) blocking antibody (PD-1 inhibitor) or programmed death-ligand 1 (PD-L1) blocking antibody (PD-L1 inhibitor) therapy (see *Appendix 1*).

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy services considers Zynyz (retifanlimab-dlwr) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Zynyz (retifanlimab-dlwr) will be authorized for 24 weeks in quantities up to 500 mg every four weeks, until disease progression, or for up to 24 months.

C. Reauthorization: Authorization **shall** be reviewed at least every 24 weeks for documented benefit. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met. Specifically, documentation that the medication is providing clinical benefit, including disease stability or improvement, and lack of disease progression, based on an assessment of change in tumor burden. If there is documentation of potential disease progression, a shortened authorization (up to three months) may be approved to allow time for clarification of response to Zynyz (retifanlimab-dlwr), including clinical re-evaluation of the patient and reimaging.

PLEASE NOTE: Additional doses of Zynyz (retifanlimab-dlwr) will not be authorized without a documented recent assessment by the treating provider (such as oncologist) with objective evidence of response to therapy, such as by re-imaging and use of iRECIST criteria.

IV. Zynyz (retifanlimab-dlwr) is considered investigational when used for all other conditions.

Position Statement

Summary

- Zynyz (retifanlimab-dlwr) is an intravenously administered programmed death receptor-1 (PD-1) blocking antibody. It is indicated for the treatment of adult patients with metastatic or recurrent locally advanced Merkel cell carcinoma (MCC), an aggressive form of skin cancer.
- The intent of this policy is to allow for coverage of Zynyz (retifanlimab-dlwr) as a front-line therapy for patients with MCC that is not amenable to curable surgery or radiation.
- Zynyz (retifanlimab-dlwr) received FDA *accelerated* approval based on a small, single-arm study in patients with advanced MCC who had not received prior systemic therapy for their disease. The study evaluated tumor response as the primary endpoint. Tumor response has not been shown to accurately predict improvement in any important clinical outcome such as overall survival. Additional controlled studies are needed to confirm whether Zynyz (retifanlimab-dlwr) provides a clinical benefit in patients with MCC.
- Bavencio (avelumab) and Keytruda (pembrolizumab) were also approved for use in advanced MCC via the FDA *accelerated* pathway based on a similar, low-quality evidence.
- As with other PD-1/PD-L1 inhibitors, the primary adverse effects of concern with Zynyz (retifanlimab-dlwr) are immune-mediated toxicities (e.g., endocrinopathies, colitis, hepatitis).
- The National Comprehensive Cancer Network (NCCN) guideline includes Zynyz (retifanlimab-dlwr) among its recommendations for front-line treatment of advanced MCC that is not amenable to curable surgery or curable radiotherapy.
- Zynyz (retifanlimab-dlwr) was studied and FDA-approved in a dose of 500 mg given intravenously every four weeks until disease progression, or for up to 24 months.
- The safety and effectiveness of Zynyz (retifanlimab-dlwr) have not been adequately studied in other disease settings. Therefore, use in settings other than that which is described above are considered investigational.
- *Reauthorization Criteria*: When coverage criteria are met, Zynyz (retifanlimab-dlwr) is authorized for six months (24 weeks) of therapy, after which time documentation must be provided to establish that the medication is effective. Specifically, there must be documentation of clinical benefit, including disease stability or improvement and there is a lack of disease progression, based on an assessment of change in tumor burden.
  * The standard of care for evaluation of response to cancer immunotherapy, such as Zynyz (retifanlimab-dlwr), is use of the iRECIST criteria for assessment of tumor burden. [1]
  * The iRECIST criteria include use of quantitative and qualitative criteria for assessment of change in tumor burden for target lesions and non-target lesions. [2]
    - Quantitative measurements for target lesions (tumor size and % change)
    - Qualitative evaluation for non-target lesions (present/disappeared/ unequivocal progression)
  * Documentation of benefit must include an assessment of the most recent imaging ("restaging scans") by the treating oncologist. Given the complexity of the evaluation, including use of the iRECIST criteria, Zynyz (retifanlimab-dlwr) will

not be reauthorized without an assessment of response to therapy, such a partial response (iPR), complete response (iCR), or stable disease (iSD).

* Use of immunotherapy may result in pseudoprogression, due to immune and T-cell activation, which can appear similar to tumor flare. If there is documentation of potential disease progression ["unconfirmed progressive disease (iUPD)"], a shortened authorization (up to three months) may be approved to allow time for clarification of response to Zynyz (retifanlimab-dlwr), including clinical re-evaluation of the patient and reimaging. Guidelines recommend reimaging for iUPD after 4-8 weeks.
* If a patient has confirmed, unequivocal new lesions (progression of disease, iPD), additional Zynyz (retifanlimab-dlwr) is not coverable. If a new lesion is equivocal, iUPD reassessment by the treating oncologist with repeat imaging would apply (as noted above).

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Background [3 4]

- Merkel cell carcinoma (MCC) is a rare, aggressive neuroendocrine carcinoma of the skin. It predominantly affects older adults (mean age of 75 years) with light skin types.
- Localized disease can generally be cured with surgical excision and radiotherapy. For patients with locally advanced or metastatic disease that is not amenable to curative surgery or radiation, systemic therapy may be used.

Clinical Efficacy [5-7]

- The efficacy of Zynyz (retifanlimab-dlwr) was evaluated in a single-arm, open-label study in adults with recurrent locally advanced or metastatic MCC. The study evaluated tumor response as a primary surrogate endpoint.
    * The MCC was not amenable to curable surgical resection or radiotherapy.
    * No prior systemic therapies, including prior programmed death receptor-1 (PD-1) blocking antibodies, were allowed in the study population.
    * Zynyz (retifanlimab-dlwr) was used as monotherapy.
    * The reported objective response rate (ORR) was 52% with 18% complete responses.
    * The duration of response was 6 months or longer in 76% of patients and 12 months or longer in 62% of patients.
- The evidence for Bavencio (avelumab) and Keytruda (pembrolizumab) in advanced MCC is also based on small, single-arm studies that evaluated ORR as a surrogate endpoint. There is no outcomes evidence for any of the PD-1 inhibitors approved for use in MCC.

Guidelines [4]

- The National Comprehensive Cancer Network (NCCN) Merkel cell carcinoma guideline lists Zynyz (retifanlimab-dlwr) among potential systemic therapeutic options that can be used for locally advanced and metastatic MCC. Bavencio (avelumab) and Keytruda (pembrolizumab) are also potential treatment options.

Investigational Uses [8]

- Zynyz (retifanlimab-dlwr) is currently being studied in several other types of cancer including anal carcinoma and gastroesophageal adenocarcinoma. However, to date, Zynyz (retifanlimab-dlwr) has not been shown to be an effective therapy for any other type of cancer.

Safety [5]

- The primary adverse effects (AEs) of interest for Zynyz (retifanlimab-dlwr) include immune-mediated reactions and infusion reactions. Immune-related AEs can affect any organ system or tissue (e.g., colitis, endocrinopathies, hepatitis, nephritis with renal dysfunction, dermatologic reactions, pneumonitis).
- Overall, the safety of Zynyz (retifanlimab-dlwr) is similar to other PD-1 and PD-L1 inhibitors.

Dosing [5]

- Zynyz (retifanlimab-dlwr) is approved at a dose of 500 mg administered intravenously (IV) every 28 days.
- In the clinical trial, Zynyz (retifanlimab-dlwr) was given until disease progression or for up to a maximum of 24 months.

Appendix 1: FDA-Approved PD-1 and PD-L1 Blocking Monoclonal Antibody Therapies [a]
Programmed death receptor-1 (PD-1) inhibitors
Jemperli (dostarlimab)
Keytruda (pembrolizumab
Libtayo (cemiplimab)
Loqtorzi (toripalimab)
Opdivo (nivolumab)
Tevimbra (tislelizumab)
Zynyz (retifanlimab-dlwr)
Programmed death-ligand 1 (PD-L1) inhibitors
Bavencio (avelumab)
Imfinzi (durvalumab)
Tecentriq (atezolizumab)

[a] Or as listed on the FDA.gov website

Cross References
Bavencio, avelumab, Medication Policy Manual, Policy No. dru499
Keytruda, pembrolizumab, Medication Policy Manual Policy No. dru367

References

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Revision History

Revision Date	Revision Summary
9/19/2024	• **Effective 1/1/2025:** Changed reauthorization from 'may' to 'shall.' Operationally, all approvals will be for 24 weeks (6 months). Ongoing therapy (beyond 24 weeks) will be subject to reauthorization review every 24 weeks, for documentation of disease stability or improvement and lack of disease progression.
12/7/2023	No criteria changes with this annual review.
6/15/2023	New policy (effective 7/15/2023) limits coverage of Zynyz (retifanlimab-dlwr) to patients with locally advanced or metastatic Merkel cell carcinoma (MCC) as a front-line therapy (no prior chemotherapy or immunotherapy).

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Medication Policy Manual

Policy No: dru753

Topic: Medications for multiple sclerosis

Date of Origin: September 1, 2023

- Aubagio, teriflunomide
- Avonex, interferon beta-1a
- Bafiertam, monomethyl fumarate
- Betaseron, interferon beta-1b
- Briumvi, ublituximab-xiiy
- Copaxone, glatiramer acetate
- Extavia, interferon beta-1b
- Gilenya, fingolimod
- Kesimpta, ofatumumab
- Lemtrada, alemtuzumab
- Mavenclad, cladribine
- Mayzent, siponimod
- natalizumab (Tysabri, Tyruko)
- Ocrevus, ocrelizumab
- Plegridy, peginterferon beta-1a
- Ponvory, ponesimod
- Rebif, interferon beta-1a
- Tascenso ODT, fingolimod
- Tecfidera, dimethyl fumarate
- Vumerity, diroximel fumarate
- Zeposia, ozanimod

Committee Approval Date: October 10, 2024

Next Review Date: 2024

Effective Date: December 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Medications in this policy are used primarily in the treatment of multiple sclerosis (MS). They help to slow the progression of disability and reduce the number of clinical relapses associated with this condition. Zeposia (ozanimod) can also be used for ulcerative colitis, and natalizumab (Tysabri/Tyruko) for Crohn's disease.

PLEASE NOTE:

This policy does NOT apply to Campath (alemtuzumab), which is used primarily in the treatment of cancer (leukemia).

Policy/Criteria

Most contracts require pre-authorization approval of medications for multiple sclerosis (MS) prior to coverage.

I. Continuation of therapy (COT): Medications for MS may be considered medically necessary for COT when criterion A **and** B below are met.

A. One of the following (1, 2, or 3) are met:

1. For diagnoses NOT listed in the coverage criteria below, full policy criteria must be met for coverage.

OR

2. For diagnoses listed in the coverage criteria below, criteria a, b, and c must be met:

a. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

b. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

AND

c. For **use of branded Aubagio, Copaxone, Gilenya, Tascenso ODT, or Tecfidera:** There is clinical documentation (including, but not limited to chart notes) of an intolerance or contraindication to an inactive ingredient in the generic equivalent medication (teriflunomide, fingolimod, glatiramer acetate/Glatopa, or dimethyl fumarate).

OR

3. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission. **For use of branded Aubagio, Copaxone, Gilenya, Tascenso ODT, or Tecfidera:** There is clinical documentation (including, but not limited to chart notes) of an intolerance or contraindication to an inactive ingredient in the generic equivalent medication (teriflunomide, glatiramer acetate/Glatopa, fingolimod or dimethyl fumarate).

AND

B. For provider-administered medications **Briumvi (ublituximab-xiiy) and Ocrevus (ocrelizumab) only:** Site of care administration requirements are met [refer to Medication Policy Manual, Site of Care Review, dru408]. PLEASE NOTE: Not all provider-administered medications in this policy are part of the site of care program. Verify with the posted site of care review policy, dru408.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Medications for MS may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that one of the following criterion A through E below are met.

A. A diagnosis of a **relapsing form of MS** (see *Appendix B*) that has been established by a specialist in neurology or MS and the following criteria 1 through 4 below are met.

1. Treatment with **at least one** low-cost disease modifying therapy (DMT) for MS (as listed in Table 1) was ineffective, contraindicated or not tolerated. Ineffectiveness is defined as meeting **at least one** of the following criteria during treatment with one of these medications:

a. The patient continues to have clinical relapses (at least one relapse within the past 12 months).

b. The patient continues to have CNS lesion progression as measured by MRI.

c. The patient continues to have worsening disability. Examples of worsening disability include, but are not limited to, decreased mobility, decreased ability to perform activities of daily living due to **disease progression, or an increase in EDSS score**.

Table 1. Low-Cost Disease Modifying Therapies (DMTs) for MS*

Teriflunomide (generic for Aubagio)
Dimethyl fumarate (generic for Tecfidera)
Fingolimod (generic for Gilenya)
Glatiramer acetate (generic for Copaxone) or Glatopa

* DMTs in this table are available without a prior authorization (PA).

AND

2. ***For non-preferred brand medications for MS only:*** Treatment with **at least one** preferred higher-cost DMT for MS (as listed in Table 2 below) has been ineffective, contraindicated, or not tolerated. Ineffectiveness is defined as meeting **at least one** of the following criteria during treatment with one of these medications:

a. The patient continues to have clinical relapses (at least one relapse within the past 12 months).

b. The patient continues to have CNS lesion progression as measured by MRI.

c. The patient continues to have worsening disability. Examples of worsening disability include, but are not limited to, decreased mobility, decreased ability to perform activities of daily living due to **disease progression, or an increase in EDSS score.**

Table 2. Preferred Higher-Cost Disease Modifying Therapies (DMTs) for MS

Briumvi (ublituximab-xiiy)
Interferon beta-1a (Avonex, Rebif)
Kesimpta (ofatumumab)
Ocrevus (ocrelizumab)
Rituximab
Natalizumab (Tysabri/Tyruko)
Zeposia (ozanimod)

For Bafiertam, Extavia, Mayzent, Ponvory, and Vumerity only: There are adjudicated and paid claims in the member's prescription history of the step therapy medications listed in *Appendix C*.

AND

3. ***For use of branded Aubagio (teriflunomide), Copaxone (glatiramer acetate), Gilenya or Tascenso ODT (fingolimod), and Tecfidera (dimethyl fumarate) only*:** There is clinical documentation (including, but not limited to chart notes) of an intolerance or contraindication to an inactive ingredient in the generic equivalent medication (teriflunomide, fingolimod, glatiramer acetate/Glatopa, or dimethyl fumarate).

AND

4. ***Briumvi (ublituximab-xiiy) and Ocrevus (ocrelizumab) only*:** Site of care administration requirements are met [refer to Medication Policy Manual, Site of Care Review, dru408].

OR

B. ***Natalizumab (Tysabri/Tyruko), Ocrevus (ocrelizumab), Briumvi (ublituximab), or Kesimpta (ofatumumab) only:*** A diagnosis of a **particularly aggressive relapsing form of MS** when established by a specialist in neurology or MS when criteria **1 AND 2** below are met.

1. The patient has had a particularly aggressive initial disease course, as defined by meeting at least one of the following:

a. An EDSS score of ≥ 4 within 5 years of onset.

OR

b. Multiple (two or more) relapses with incomplete resolution in the past year.

OR

c. At least two MRI studies showing new or enlarging T2 lesions or gadolinium-enhancing lesions despite treatment over 6 months.

OR

d. The presence of spinal or brainstem lesions on MRI.

AND

2. ***For Briumvi (ublituximab) and Ocrevus (ocrelizumab) only:*** The Site of Care administration requirements are met [refer to Medication Policy Manual, Site of Care Review, dru408].

OR

C. ***Ocrevus (ocrelizumab) only:*** A diagnosis of a **primary progressive MS** when criteria 1 and 2 below are met.

1. A diagnosis of **primary progressive MS** (see *Appendix B*) when established by a specialist in neurology or MS.

AND

2. The Site of Care administration requirements are met [refer to Medication Policy Manual, Site of Care Review, dru408].

OR

D. ***Zeposia (ozanimod) only:*** A diagnosis of **ulcerative colitis** (UC) when following criteria 1 through 3 below are met.

1. A diagnosis of **ulcerative colitis** (UC) when established by or in consultation with a specialist in gastroenterology.

AND

2. Severity Criteria: At least one of the following criterion a, b, or c below, are met.

a. Treatment with an adequate course of corticosteroids (for example, prednisone 40 to 60 mg/day, oral budesonide 9 mg/day, or budesonide rectal for 7 to 14 days) was ineffective or is contraindicated.

OR

b. The patient has been unable to taper an adequate course of corticosteroids without experiencing worsening of disease.

OR

c. The patient is experiencing breakthrough disease (for example, active disease flares) while stabilized on a conventional immunomodulators, for at least two months. Conventional immunomodulators for UC include azathioprine, balsalazide, cyclosporine, mercaptopurine, mesalamine, and sulfasalazine.

AND

3. Treatment with two of the following preferred products listed in Table 3 below was not effective after at least a 12-week treatment course unless not tolerated or contraindicated:

Table 3. Ulcerative Colitis (UC) – Preferred Products

Adalimumab (Humira, or biosimilars)

Skyrizi (risankizumab)
Stelara (ustekinumab)
Tremfya (guselkumab)
Tofacitinib (Xeljanz/Xeljanz XR)
Rinvoq (upadacitinib)

OR

E. ***Natalizumab (Tysabri/Tyruko) only:*** A diagnosis of **Crohn's disease** when following criteria 1 through 3 are met.

1. Natalizumab (Tysabri/Tyruko) is prescribed by, or in consultation with, a specialist in gastroenterology for the indication of Crohn's disease.

AND

2. Adalimumab (Humira or biosimilars) is not effective after at least an initial 3-dose induction period, except if not tolerated due to documented clinical side effects.

AND

3. Infliximab is not effective after at least an initial induction period (5 mg/kg on weeks 0, 2 and 6), except if not tolerated due to documented clinical side effects.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers oral and subcutaneous (SC) self-injectable medications [as listed in Table 4] for multiple sclerosis coverable only under the pharmacy benefit (as self-administered medications).

B. Regence Pharmacy Services considers intravenous (IV) infused medications [as listed in Table 4] for multiple sclerosis coverable only under the medical benefit (as a provider-administered medication).

C. When pre-authorization is approved, each drug will be covered in the following quantities and for the following authorization periods outlined in Table 4 below:

Table 4: Medications for MS Quantity Limits, Authorization Period, and Route of Administration

Product	Quantity Limit and Authorization Period	Route/Benefit
Aubagio (teriflunomide)	- Up to 28 tablets per 28 days. - Authorization **shall** be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that all of the following criteria (a, b, and c) below are met: **a.** Current medical necessity criteria are met. **AND** **b.** For brand Aubagio (teriflunomide): There is an intolerance or	Oral; pharmacy benefit

Product	Quantity Limit and Authorization Period	Route/Benefit
	contraindication to an <u>inactive</u> ingredient in generic teriflunomide. **AND** **c.** Ongoing clinical benefit, such as disease stability or improvement.	
Avonex (interferon beta-1a)	- Up to 4 syringes per 28 days. - Authorization may be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.	SC; pharmacy benefit
Bafiertam (monomethyl fumarate)	- Up to 120 capsules per 30 days. - Authorization may be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.	Oral; pharmacy benefit
Betaseron (interferon beta-1b)	- Up to 15 syringes every 30 days. - Authorization may be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.	SC; pharmacy benefit
Briumvi (ublituximab-xiiy)	- <u>Initial authorization (first 12 months)</u>: Up to 1500 mg (10 vials) for the first 12 months (one IV infusion of 150 mg on day 1 followed by a second infusion of 450 mg on day 15 with subsequent doses of 450 mg infusions given at 24 weeks intervals from the first infusion). - <u>Additional 12-month authorization:</u> Up to quantities of 900 mg (6 vials) every 12 months. (450 mg infusions every 24 weeks). - Authorization may be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.	IV; medical benefit (**SOC program applies)**
Copaxone, (glatiramer acetate)	- <u>Copaxone 20 mg/mL</u>: Up to 30 syringes per 30 days. - <u>Copaxone 40 mg/mL</u>: Up to 12 syringes per 28 days. - Authorization **shall** be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that all of the following (a, b, and c) are met: **a.** Current medical necessity criteria are met. **AND** **b.** For brand Copaxone: There is an intolerance or contraindication to an <u>inactive</u> ingredient in generic glatiramer acetate. **AND** **c.** Ongoing clinical benefit, such as disease stability or improvement	SC; pharmacy benefit

Product	Quantity Limit and Authorization Period	Route/Benefit
Extavia (interferon beta-1b)	- Up to 15 pre-filled syringes per 28 days. - Authorization may be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.	SC; pharmacy benefit
Fingolimod (Gilenya or Tascenso ODT)	- Up to 30 capsules or oral disintegrating tablets per 30 days. - Authorization **shall** be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that all of the following (a, b, and c) are met: **a.** Current medical necessity criteria are met. **AND** **b.** For brand fingolimod (Gilenya or Tascenso ODT): There is an intolerance or contraindication to an inactive ingredient in generic fingolimod. **AND** **c.** Ongoing clinical benefit, such as disease stability or improvement.	Oral; pharmacy benefit
Kesimpta (ofatumumab)	- Initial year: Up to 15 pen injectors per year. - Subsequent years: Up to 13 pen injectors per year. - Authorization may be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement	SC; pharmacy benefit
Lemtrada (alemtuzumab)	- Initial authorization (first treatment course; 5 doses): Up to 12 mg/day IV infusion on five consecutive days in a 12-month period. - Second authorization (second treatment course; 3 doses): Following the first treatment course (of five doses), a second treatment course of up to 12 mg/day on three consecutive days in a 12-month period. - Additional Authorizations [additional treatment course(s); 3 doses]: Following the second treatment course (of three doses), subsequent treatment courses of 12 mg/day on three consecutive days may be administered in a 12-month period. - All subsequent courses must be administered at least 12 months after the last dose of the prior treatment course. - Authorization **shall** be reviewed after each treatment course. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.	IV; medical benefit
Mavenclad (cladribine)	- Up to 20 tablets per year for up to a maximum of 2 years only. - Use of Mavenclad (cladribine) beyond the 2-year course is considered investigational.	Oral; pharmacy benefit

Product	Quantity Limit and Authorization Period	Route/Benefit
	- Authorization **shall** be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement	
Mayzent (siponimod)	- For initial 5-day dose titration: Up to one Starter pack. - Maintenance dosing: Up to 120 of the 0.25 mg tablets, or 30 of the 1mg or 2 mg tablets per 30 days, based on a recommended maintenance dose of 1 to 2 mg per day depending on CYP2C9 genotype. - Authorization may be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.	Oral; pharmacy benefit
Ocrevus (ocrelizumab)	- Initial authorization (first 12 months): Up to 1200 mg (4 vials) for the first 12 months (one IV infusion of 300 mg on day 1 followed by a second 300 mg infusion on day 15 with subsequent doses of 600 mg infusions every 6 months thereafter). - Additional 12-month authorization: Up to quantities of 1200 mg (4 vials) every 12 months (600 mg infusions (2 vials) every 6 months). - Authorization may be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement	IV; medical benefit (**SOC program applies)**
Plegridy (peginterferon beta-1a)	- Up to 2 syringes per 28 days. - Authorization may be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement	SC; pharmacy benefit
Ponvory (ponesimod)	- For initial 14-day dose titration: Up to one Starter pack. - Maintenance dosing: Up to thirty 20 mg tablets per 30 days, based on a recommended maintenance dose of 20 mg once daily. - Authorization may be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.	Oral; pharmacy benefit
Rebif (interferon beta-1a)	- Up to 12 syringes per 28 days. - Authorization may be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement	SC; pharmacy benefit

Product	Quantity Limit and Authorization Period	Route/Benefit
Tecfidera (dimethyl fumarate)	- Up to 60 capsules per 30 days. - Authorization **shall** be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that all of the following (a, b, and c) are met: **a.** Current medical necessity criteria are met. **AND** **b.** For brand Tecfidera (dimethyl fumarate): There is an intolerance or contraindication to an inactive ingredient in generic dimethyl fumarate. **AND** **c.** Ongoing clinical benefit, such as disease stability or improvement.	Oral; pharmacy benefit
Natalizumab (Tysabri/Tyruko)	- Up to one 300-mg IV infusion every 4 weeks. - **Multiple sclerosis:** Authorization may be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement. - **Crohn's disease:** Initial authorization **shall** be reviewed at 12 weeks. Continued authorization shall be reviewed at least every six months. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.	IV; medical benefit
Vumerity (diroximel fumarate)	- Up to 120 capsules per 30 days. - Authorization may be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.	Oral; pharmacy benefit
Zeposia (ozanimod)	- Up to 30 capsules per 30 days. - Authorization may be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.	Oral; pharmacy benefit

IV. Medications for MS are considered not medically necessary when used in the follow settings:

A. ***For natalizumab (Tysabri/Tyruko) only*** when used in the following settings:

1. For the treatment of Crohn's disease when used concomitantly with any of the following:

a. Adalimumab.
b. Infliximab.
c. Cimzia (certolizumab pegol).

2. For the treatment of ulcerative colitis.

V. Medications for MS are considered investigational when used for all other conditions, including but not limited to:

A. Concomitantly with any other DMTs for MS (see *Appendix A*).

B. For non-relapsing forms of MS, such as SPMS without active relapses OR primary progressive MS (PPMS), unless specifically noted in the coverage criteria above, such as for Ocrevus, ocrelizumab.

C. Any cancer indication, including, but not limited to B-cell chronic lymphocytic leukemia.

D. **For Lemtrada (alemtuzumab):** Post-transplant antibody induction therapy.

E. **For Ocrevus (ocrelizumab):** Neuromyelitis Optica Spectrum Disorders (NMOSD).

F. **For Ocrevus (ocrelizumab) and natalizumab (Tysabri/Tyruko):** Rheumatoid arthritis.

Position Statement

Summary

- There are many medications for multiple sclerosis (MS) treatment. Medications for MS have different routes of administration as well as mechanisms of action. These disease modifying therapies (DMTs) help to decrease the number of clinical exacerbations associated with this condition and slow the progression of disability.
- Zeposia (ozanimod) has been proven to be effective in ulcerative colitis (UC), while natalizumab (Tysabri/Tyruko) has proven efficacy in Crohn's disease, with both having FDA approvals in these respective diseases.
- The intent of this policy is to allow for coverage of medications for MS in the settings where they have been proven safe and effective, when lower cost preferred options (as listed in the coverage criteria) are ineffective or not a treatment option (as described in coverage criteria).
- MS consists of two main clinical courses of disease, relapsing or primary progressive (see *Appendix B)* [1 2]:
    * Relapsing forms of MS include clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), and active secondary progressive MS (SPMS). CIS is the first clinical presentation that shows characteristics of inflammatory demyelination that could be MS, but not a definitive diagnosis of MS. All of the medications for MS are FDA approved for use in relapsing forms of MS. Rituximab may also be used off label for the treatment of relapsing forms of MS.
    * Primary progressive MS (PPMS) is the defined as progression of disability without relapses. Only Ocrevus (ocrelizumab) is FDA approved for use in PPMS.
- American Academy of Neurology (AAN) guidelines state[2]:
    * DMTs should be offered to patients with relapsing forms of MS.
    * Guidelines state the choice of initial DMT should be individualized to consider of safety, route of administration, lifestyle, cost, efficacy, adverse effects (AEs), and tolerability.
    * Disease activity, adherence, AE profiles, and mechanism of action should be considered when switching DMTs.
    * Natalizumab (Tysabri/Tyruko), fingolimod (generic, Gilenya, and Tascenso ODT), or Lemtrada (alemtuzumab) should be used in patients with highly active disease based on improved efficacy in this subgroup.
- Individual responses and tolerability of DMTs are unpredictable and may vary between patients. If one DMT provides an inadequate response, another DMT may be effective.
- There is limited evidence of increased efficacy or safety between the majority of medications for MS in reducing signs and symptoms of MS or slowing progression of disease due to a lack of head-to-head trials; therefore, the medication with lowest cost often provides the best value for members.
    * Fingolimod (generic, Gilenya, and Tascenso ODT), Zeposia (ozanimod), and Mayzent (siponimod) belong to a class of medications called sphingosine 1-phosphate (S1P) receptor modulators. Of the three, fingolimod (generic) provides the best value.
    * Dimethyl fumarate (generic, Tecfidera), Vumerity (diroximel fumarate), and Bafiertam (monomethyl fumarate) belong to a class of medications called

fumarates, of which dimethyl fumarate (generic) provides the best value.

* Currently, three glatiramer-containing products are available: Copaxone, generic glatiramer, and Glatopa. Generic glatiramer and Glatopa provide the best value to members of this health plan.

- Lemtrada (alemtuzumab) is not recommended as a first- or second-line option due to serious safety concerns[3].
  * Lemtrada (alemtuzumab) has boxed warnings describing an increased risk of autoimmunity, infusion reactions, and malignancies with its use. The FDA labeling states that it should generally be reserved for patients who have had an inadequate response to two or more DMTs for MS.
  * Because of these safety concerns, distribution of Lemtrada (alemtuzumab) is restricted with a REMS program for prescribers, health care facilities, and pharmacies.
- The safety and effectiveness of combination use of disease modifying therapies for MS medications has not been established.
- Medications for MS may be covered at the doses proven to be safe and effective in the clinical trials (as outlined in Table 4 of the coverage criteria above). The safety and effectiveness of higher doses has not been established.
- Use of medications for MS in clinical settings other than described in the coverage criteria is considered investigational.

Clinical Efficacy:

RELAPSING REMITTING MS

Lemtrada (alemtuzumab) for Relapsing Remitting MS (RRMS)[4-6]

- Two, randomized, open-label, rater-blinded, 2-year, studies compared Lemtrada (alemtuzumab) with interferon beta-1a in patients with relapsing-remitting multiple sclerosis (RRMS).
  * The CARE-MS I trial included previously untreated patients while CARE-MS II trial included patients who had at least one relapse while on an interferon beta product or glatiramer acetate.
  * In each trial, there was a statistically significantly lower annualized relapse rate for patients treated with Lemtrada (alemtuzumab) (22%-35%) compared to interferon beta-1a (40%-51%).
  * Treatment-experienced patients treated with Lemtrada (alemtuzumab) experienced a statistically significant reduction in the rate of disease progression compared to those treated with interferon beta 1a (13% vs 20%, p=0.008). The difference in rates of disease progression was not statistically significant among treatment-naïve patients.
- Extension studies for Lemtrada (alemtuzumab) suggest that efficacy is maintained through at least year five but certain patients with disease activity may require additional courses. Among patients who completed CARE-MS II, 58.0% received just no additional courses of alemtuzumab while 30.1% received one additional course at some point in the five-year follow-up period. The most common reason for additional courses was relapse.

Interferon-beta for RRMS

- There are several randomized, controlled trials comparing the efficacy of the different

interferon beta products in the treatment of relapsing-remitting multiple sclerosis, with all of them favoring interferon-beta treatment over placebo for reducing relapse rate.

Glatiramer acetate (generic, Copaxone, and Glatopa) for RRMS[7]

- The efficacy of glatiramer acetate was evaluated in five studies in patients with relapsing-remitting MS. The first four studies compared daily glatiramer to placebo and the other studies compared three times weekly glatiramer to placebo.
- Results demonstrated that glatiramer acetate was superior to placebo in reducing the number of relapses.

Teriflunomide (generic, Aubagio) for RRMS[8]

- The efficacy of teriflunomide was evaluated in three studies in patients with relapsing-remitting MS. These studies compared daily teriflunomide (7 mg or 14 mg) to placebo.
- Results demonstrated that teriflunomide was superior to placebo in reduction of annualized relapse rate and relative risk of disease progression at 108 weeks.

Fingolimod (generic, Gilenya, and Tascenso ODT) for RRMS[9 10]

- The efficacy of fingolimod was evaluated in three phase 3 studies in patients with relapsing-remitting MS. The first study compared fingolimod to placebo and the two other studies compared fingolimod to interferon beta-1a.
- Results demonstrated that fingolimod was superior to placebo and interferon beta-1a in reducing annualized relapse rates.

Mayzent (siponimod) for RRMS[11]

- Siponimod was studied in one phase 3 study in patients with SPMS with or without ongoing relapses.
    * Mayzent (siponimod) met its primary endpoint of slowing the time to 3-month confirmed disability progression (CDP). However, the key secondary endpoint of time to 20% worsening in the timed 25-foot walk test (T25FW) was not met.
    * In subgroup analyses, it was observed that efficacy was primarily in patients who were younger, had active relapses, and had active MRI lesions. This population likely had a relapsing form of MS rather than non-active SPMS, thus efficacy in non-active SPMS is unclear and further studies are needed.

Zeposia (ozanimod) for RRMS[12 13]

- Zeposia (ozanimod) was evaluated in two phase 3 studies in patients with relapsing forms of MS. Both studies compared Zeposia (ozanimod) to interferon beta-1a.
- Results showed that Zeposia (ozanimod) was superior to interferon beta-1a in reducing annualized relapse rates. However, pooled results from both studies showed that there was no improvement in disability progression over interferon beta-1a.

Ponvory (ponesimod) for RRMS[14]

- The efficacy of ponesimod was evaluated in one phase 3 study in patients with relapsing-remitting MS. The study compared daily ponesimod (Ponvory) to Aubagio (teriflunomide) for 108 weeks.
- Results demonstrated that ponesimod (Ponvory) was superior to teriflunomide (Aubagio) in reducing annualized relapse rates.

Mavenclad (cladribine) for RRMS[15]

- The efficacy of Mavenclad (cladribine) was evaluated in one phase 3 study in patients with relapsing-remitting MS. The study compared Mavenclad (cladribine) to placebo for 96 weeks.

- Results demonstrated that Mavenclad (cladribine) was superior to placebo in reducing annualized relapse rates.

Dimethyl fumarate (generic, Tecfidera), diroximel fumarate (Vumerity), and Bafiertam (monomethyl fumarate) for RRMS[16-18]

- The efficacy of dimethyl fumarate was evaluated in two phase 3 studies in patients with relapsing-remitting MS. Both studies compared dimethyl fumarate to placebo.
- Results demonstrated that dimethyl fumarate was superior to placebo in reducing annualized relapse rates.
- The efficacy of Vumerity (diroximel fumarate) was based on bioavailability studies in patients with RRMS and healthy patients comparing oral dimethyl fumarate to oral diroximel fumarate capsules.
- The efficacy of Bafiertam (monomethyl fumarate) was based on bioavailability studies in healthy patients, The studies demonstrated the bioequivalence of Bafiertam (monomethyl fumarate) to oral Tecfidera (dimethyl fumarate).

Kesimpta (ofatumumab) for RRMS[19]

- The efficacy of Kesimpta (ofatumumab) was evaluated in two phase 3 studies in patients with relapsing-remitting MS. The study compared Kesimpta (ofatumumab) to Aubagio (teriflunomide).
- Results demonstrated that Kesimpta (ofatumumab) was superior to teriflunomide (Aubagio) in reducing annualized relapse rates.

Briumvi (ublituximab-xiiy) for RRMS[20-22]

- Briumvi (ublituximab-xiiy) has been shown to significantly reduce annual relapse rate (ARR) and slow worsening of disease based on MRI outcomes in patients with relapsing forms of MS when compared to Aubagio (teriflunomide).
    * Two identical, phase 3, randomized, double-blind, double dummy, active control 96-week studies (ULTIMATE I and ULTIMATE II, total N=1089), evaluated the effects of Briumvi (ublituximab-xiiy) compared to Aubagio (teriflunomide) in patients with relapsing forms of MS. Briumvi (ublituximab-xiiy) was significantly superior to teriflunomide in reducing annualized relapse (relative risk reduction of 59% in ULTIMATE I and 49% in ULTIMATE II). On MRI outcomes, the patients in the Briumvi (ublituximab-xiiy) groups had significantly fewer new and/or enlarging T2 lesions, and less T1 lesions relative to the Aubagio (teriflunomide) groups.

Ocrevus (ocrelizumab) for RRMS[23 24]

- Ocrevus (ocrelizumab) has been shown to reduce elapse rate, slows disability progression, and slows worsening of disease based on MRI outcomes in patients with relapsing forms of MS.
    * Two identical, 96-week studies (OPERA I and OPERA II) evaluated the effects of Ocrevus (ocrelizumab) compared to Rebif (interferon beta-1a) in patients with relapsing forms of MS. Ocrevus (ocrelizumab) was superior to interferon beta-1a in reducing annualized relapse and in slowing confirmed disability progression. On MRI, the patients in the Ocrevus (ocrelizumab) group had fewer new and/or enlarging T2 lesions, less T1 lesions, and a reduced rate of total brain volume loss relative to the Rebif (interferon beta-1a) group.

Natalizumab(Tysabri/Tyruko) for RRMS[2 25 26]

- The efficacy of natalizumab (Tysabri/Tyruko) was evaluated in two phase 3 studies in patients with relapsing-remitting MS. The two studies compared natalizumab to placebo.
- Results demonstrated that natalizumab was superior to placebo in reducing annualized relapse rates and lowering the rate of disability.
- AAN guidelines state that natalizumab (Tysabri/Tyruko), fingolimod (generic, Gilenya, Tascenso ODT), or Lemtrada (alemtuzumab) should be used in patients with highly active disease.
- Although no specific guidelines exist, proposed definitions of aggressive or highly active have been developed. It may be defined as at least one of the following: an EDSS score of 4 within 5 years of onset, multiple (two or more) relapses with incomplete resolution over a one-year period, more than two MRI studies showing new or enlarging T2 lesions or gadolinium-enhancing lesions despite treatment, no response to therapy with one or more disease-modifying therapies for up to 1 year, or the presence of spinal lesions. Monitoring for treatment efficacy via MRI is recommended every 6 months.
- Natalizumab (Tysabri/Tyruko) in combination with any other disease-modifying multiple sclerosis treatment medication has not been shown to be more effective than natalizumab (Tysabri/Tyruko) alone in the treatment of multiple sclerosis and may be contraindicated due to safety concerns.

PRIMARY PROGRESSIVE MS

Ocrevus (ocrelizumab) for Primary Progressive MS (PPMS)[24 27]

- Ocrevus (ocrelizumab) has been shown to slow disability progression and slow the worsening of MRI outcomes in patients with PPMS.
    * One 120-week study (ORATORIO) evaluated the effects of Ocrevus (ocrelizumab) relative to placebo in patients with PPMS. Ocrevus (ocrelizumab) was superior to placebo reducing the proportion of patients who had sustained 12-week confirmed disability progression. The treatment group also showed a significant decrease in T2 volume and showed significantly less brain volume loss on MRI.

CROHN'S DISEASE

Natalizumab (Tysabri/Tyruko) for Crohn's Disease[25 28 29]

- FDA-approval of natalizumab (Tysabri/Tyruko) in Crohn's Disease (CD) was based on three trials: two in induction of clinical response/remission and one in the maintenance of remission.
    * Patients in the induction trials had moderately to severely active CD (Crohn's Disease Activity Index [CDAI] $\geq$ 220 and $\leq$ 450).
    * In one of the two induction studies, significant differences in response to natalizumab were only observed in the subgroup of patients with elevated C-reactive protein (CRP) levels. The second induction study used elevated CRP as an entry criterion. However, other medications (e.g. prednisone) may lower CRP levels, making this an insensitive predictor of efficacy.
    * The treatment effect in the induction studies ranged from approximately 13 to 15%.
    * In the trial that looked at maintenance of response of CD over 9 to 15 months, the treatment effect was approximately 33%.

- Concomitant use natalizumab (Tysabri/Tyruko) with immunosuppressives (6-mercaptopurine, azathioprine, cyclosporine, and methotrexate) or inhibitors of TNF-α (e.g., infliximab and adalimumab) is not recommended due to potential safety concerns.
- Natalizumab (Tysabri/Tyruko) is generally considered a last-line agent for Crohn's disease due to lack of comparative efficacy with other therapies and its potential for serious safety risks.
    * Steroids, immunosuppressives, and inhibitors of TNF-alpha are recommended prior to prescribing natalizumab (Tysabri/Tyruko).
    * A study demonstrating the efficacy of Humira (adalimumab) in patients in whom Remicade (infliximab) was not effective is the basis for recommending both Humira (adalimumab) and infliximab prior to natalizumab (Tysabri/Tyruko).
        ▪ A randomized, placebo-controlled study comparing Humira (adalimumab) with placebo in 325 patients with Crohn's disease who had lost response to treatment with, or were intolerant to, previous Remicade (infliximab) therapy demonstrated induction of remission in 21% versus 7% of patients who had received adalimumab and placebo, respectively ($p<0.001$, ABI 14%, NNT=8).
- One small trial (n = 79) studied the concomitant use of natalizumab (Tysabri/Tyruko) and Remicade (infliximab) in patients who did not achieve remission of their CD after 12 weeks of Remicade (infliximab).
    * The trial was not powered to detect differences in efficacy between treatment groups.
    * There were not enough patients in the study to determine whether there were differences in uncommon or rare adverse effects between treatment groups.
    * The natalizumab (Tysabri/Tyruko) prescribing information warns against use of this combination.
- Natalizumab (Tysabri/Tyruko) should be discontinued in patients with CD who:
    * Do not achieve therapeutic benefit after 12 weeks of induction therapy.
    * Cannot discontinue chronic concomitant steroids within six months of starting therapy.

<u>ULCERATIVE COLITIS</u>

<u>Zeposia (ozanimod) for Ulcerative Colitis[30]</u>

- Zeposia (ozanimod) was evaluated in the TRUE NORTH study, a phase 3 study that evaluated Zeposia (ozanimod) for the induction and maintenance of remission for UC versus placebo.
- Results showed that ozanimod improved rates of clinical response and remission compared to placebo. Improvements in histological remission and mucosal healing were also noted.
- Refer to Medication Policy Manual, Drugs for chronic inflammatory diseases, dru444 for treatment guidelines and severity criteria.

Investigational Uses

Lemtrada (alemtuzumab)[31-35]

- The Lemtrada REMS program mitigates off-label use of Lemtrada (alemtuzumab); however, it has been studied in other conditions. Due to a lack of published data, lack of high-quality data, or lack of positive data, these conditions are considered investigational. Details of select investigational uses are reported below.
- B-cell chronic lymphocytic leukemia:
  * A high dose formulation of Campath (alemtuzumab) was approved for the treatment of B-cell chronic lymphocytic leukemia (CLL) but was removed from the market in 2012 to prevent off-label use of Campath (alemtuzumab) in MS. Since 2012, Campath (alemtuzumab) has been available for very limited use in CLL through patient access programs. Lemtrada (alemtuzumab) is given at a lower dose when used for MS, lower doses are considered investigational for any other condition, including CLL and other cancers.
  * There have been no controlled clinical trials evaluating the use of low-dose (12 mg) Lemtrada (alemtuzumab) in B-cell chronic lymphocytic leukemia.
  * High-dose Campath (alemtuzumab) is available for patients with leukemia directly from the manufacturer, free of charge through patient access programs.
- Post-transplant antibody induction therapy:
  * There are no controlled clinical trials evaluating the use of low-dose (12 mg) Lemtrada (alemtuzumab) in the post-transplant setting.

Natalizumab (Tysabri/Tyruko)[25 36]

- A Risk Evaluation and Mitigation Strategy (REMS) Prescribing Program currently prevents off-label use of natalizumab (Tysabri/Tyruko).
- Authors of a small, open-label study in 10 patients with active ulcerative colitis reported clinical benefit at 4 weeks with administration of natalizumab. Larger, well-designed trials are needed before safety and efficacy are established for this indication.
- There are no data available to support the safety and efficacy of natalizumab (Tysabri/Tyruko) in the treatment of rheumatoid arthritis.

Ocrevus (ocrelizumab)[37-40]

- Due to a lack of published data, the use of Ocrevus (ocrelizumab) in conditions other than relapsing forms of MS and PPMS is considered investigational.
- Neuromyelitis optica spectrum disorders (NMOSD; previously known as Devic disease) are characterized by a combination of bilateral optic neuropathy and cervical myelopathy. While both NMOSD and MS are demyelinating diseases they are considered different diseases based on unique immunologic features and differences in imaging features, biomarkers, and neuropathology.
- Rituximab has been shown to the frequency of NMOSD relapses and neurologic disability based on results from one systematic review. However, the optimal treatment regimen and duration have not been determined and additional long-term safety experience is needed to clarify the role of rituximab as a first-line option.
- There is no published evidence to support the use of Ocrevus (ocrelizumab) for NMOSD.
- While Ocrevus (ocrelizumab) has a similar mechanism of action to rituximab, it has not been studied for the same indications. Thus, due to a lack of data, these conditions are considered investigational.

Kesimpta (ofatumumab) and Briumvi (ublituximab-xiiy)[19 41]

- Due to a lack of published data, the use of Kesimpta (ofatumumab) or Briumvi (ublituximab-xiiy) in conditions other than relapsing forms of MS is considered investigational.
- While Kesimpta (ofatumumab) and Briumvi (ublituximab-xiiy) have a similar mechanism of action to rituximab, it has not been studied for the same indications. Thus, due to a lack of data, these conditions are considered investigational.

Zeposia (ozanimod)[30]

- The use of combination (more than one) targeted immunomodulator for UC, such as Humira (adalimumab), or tofacitinib (Xeljanz/Xeljanz XR), is considered investigational. Ozanimod has only been studied as monotherapy for UC. There is no evidence supporting the safety or efficacy of combination therapy with another targeted immunomodulator.

Safety

Lemtrada (alemtuzumab)[3]

- Lemtrada (alemtuzumab) has boxed warnings for the following:
  * Sometimes fatal autoimmune conditions, such as immune thrombocytopenia and anti-glomerular basement membrane diseases.
  * Serious and life-threatening infusion reactions.
  * An increased risk of malignancies including thyroid cancer, melanoma, and lymphoproliferative disorders.
- Due to its significant safety concerns an FDA Risk Evaluation and Mitigation Strategy (REMS) program limits the availability of Lemtrada (alemtuzumab) to certified prescribers, healthcare facilities, and specialty pharmacies.
- Regular monitoring is required due to the potential for long-term adverse events. Complete blood count, serum creatinine levels, urinalysis should be collected prior to treatment and at monthly intervals. Thyroid function tests should be conducted prior to treatment and every three months thereafter. Baseline and annual skin exams should be conducted to monitor for melanoma.

Mayzent (siponimod)[42]

- Mayzent (siponimod) requires an initial 5-day dose titration period due to the risk of first-dose bradycardia. Additionally, first-dose monitoring is required for patients with sinus bradycardia, first- or second-degree atrioventricular block, or a history of myocardial infarction or heart failure.

Natalizumab (Tysabri/Tyruko))[25]

- Several cases of progressive multifocal leukoencephalopathy (PML), a progressive demyelinating disease of the CNS, have been associated with natalizumab (Tysabri/Tyruko) use. PML is an opportunistic viral infection of the brain that usually leads to death or severe disability.
- The natalizumab (Tysabri/Tyruko) prescribing information contains a Boxed Warning describing the increased risk of PML, which may lead to death or severe disability.
- Because of the risk of PML, distribution of natalizumab (Tysabri/Tyruko) is restricted via a REMS Prescribing Program.
  * Providers must register to prescribe, distribute, or infuse natalizumab (Tysabri/Tyruko).

    * Only patients who are registered with and who meet all the conditions of either the MS or CD REMS programs are eligible to receive natalizumab (Tysabri/Tyruko).

- The most common side effects observed in patients receiving natalizumab (Tysabri/Tyruko) include infections, acute hypersensitivity reactions, depression, and cholelithiasis (gall stones).
- There are several case reports of patients who developed melanoma after starting treatment with natalizumab (Tysabri/Tyruko)). Although cause-effect has not been established, clinicians should be aware of this potential risk, especially when considering therapy for patients with a history of melanoma.
- The natalizumab (Tysabri/Tyruko) prescribing information contains a warning regarding the potential for liver injury. In some patients this occurred as early as six days after an initial dose.

Appendix A: Disease-Modifying Agents Used in the Treatment of Multiple Sclerosis (MS)
Bafiertam (monomethyl fumarate)
Briumvi (ublituximab-xiiy)
Dimethyl fumarate (generic, Tecfidera)
Fingolimod (generic, Gilenya, and Tascenso ODT)
Glatiramer acetate (generic glatiramer, Glatopa, and Copaxone)
Interferon beta-1a (Avonex, Rebif)
Interferon beta-1b (Betaseron, Extavia)
Kesimpta (ofatumumab)
Lemtrada (alemtuzumab)
Mavenclad (cladribine)
Mayzent (siponimod)
Natalizumab (Tysabri/ biosimilar Tyruko)
Novantrone (mitoxantrone)
Ocrevus (ocrelizumab)
Plegridy (peginterferon beta-1a)
Ponvory (ponesimod)
Rituximab
Teriflunomide (generic, Aubagio)
Vumerity (diroximel fumarate)
Zeposia (ozanimod)

Rituximab is not FDA-approved for use in MS, but has evidence for efficacy[2]

Appendix B: Multiple Sclerosis Forms/Clinical Course Definitions[1 2]	
Clinically Isolated Syndrome (CIS)	The first clinical presentation that shows characteristics of inflammatory demyelination that could be MS.
Relapsing-remitting MS (RRMS)	Characterized by acute relapses that are followed by some degree of recovery. These attacks develop acutely, evolving over days to weeks. Over the next several weeks to months, most patients experience a recovery of function that is often (but not always) complete. Between attacks the patient is neurologically and symptomatically stable.
Secondary progressive MS (SPMS)	Defined as sustained progression of physical disability occurring separately from relapses, in patients who previously had RRMS. SPMS may be active or not active. Activity is determined by the presence of ongoing relapses or MRI activity. There are no clinical, imaging, immunologic, or pathologic criteria to determine when a patient transition from RRMS to SPMS, it is usually diagnosed retrospectively.
Primary progressive MS (PPMS)	Defined as progression of disability from onset without superimposed relapses. The AAN defines PPMS as the third clinical type characterized by a steady decline in function from the beginning without acute attacks.

Appendix C: Step Therapy Medications

Targeted Agents and GPIs/NDCs (multisource code)	Prior Agents and GPIs/NDCs (multisource code) Prerequisites	Look-Back Time Frame
• Bafiertam 62405550****** (M,N,O,Y) • Extavia 00078-0569-** (NDC) • Mayzent 62407070******(M,N,O,Y) • Ponvory 62407060****** (M,N,O,Y) • Vumerity 62405530****** (M,N,O,Y)	**ONE** of the following: • dimethyl fumarate 62405525**** (Y) • fingolimod 62407025****** (Y) • teriflunomide 62404070****** (Y) • glatiramer 62400030****** (Y) **AND** **ONE** of the following: • Avonex/Rebif 6240306045**** (M,N,O,Y) • • Kesimpta 62405065****** (M,N,O,Y) • • • Zeposia 62407050****** (M,N,O,Y)	180 days

Cross References
Site of Care Review, Medication Policy Manual, Policy No. dru408
Drugs for chronic inflammatory diseases, Medication Policy Manual, Policy No. dru444
Products with Therapeutically Equivalent Biosimilars/Reference Products, Medication Policy Manual, Policy No. dru620

Codes	Number	Description
HCPCS	J0202	Injection, alemtuzumab (Lemtrada) 1mg
HCPCS	J2323	Injection, natalizumab (Tysabri/Tyruko), 1 mg
HCPCS	J2350	Injection, ocrelizumab (Ocrevus), 1 mg
HCPCS	J2329	Injection, ublituximab-xiiy (Briumvi), 1mg
ICD-10	G35	Multiple sclerosis

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Revision History

Revision Date	Revision Summary
10/10/2024	Effective 12/1/2024: • Updated preferred options to include Skyrizi (risankizumab) and Tremfya (guselkumab) for treatment of ulcerative colitis • No change to intent.
12/7/2023	• Added newly approved Tysabri (natalizumab) biosimilar Tyruko (natalizumab) to policy. • Added Briumvi (ublituximab) and Kesimpta (ofatumumab) as options for highly active disease, no change to intent.
9/14/2023	Effective 1/1/2024, Betaseron (interferon beta-1b), Mavenclad (cladribine) and Plegridy (peginterferon beta-1a) have been moved to non-preferred.
6/15/2023	New combination policy (effective 9/1/2023): • Combined the following medication policies: dru111 Tysabri (natalizumab), dru479 Ocrevus (ocrelizumab), dru511 Non-preferred MS treatments, dru570 Non-preferred Glatiramer Products, dru674 Zeposia (ozanimod), dru739 Briumvi (ublituximab-xiiy). • Prior authorization (PA) not required for the following DMTs for MS: - Generic dimethyl fumarate, generic fingolimod, generic teriflunomide, generic glatiramer (no change to coverage). - Glatiramer (Glatopa) (changed to "no PA required"). • Change in PA requirements for relapsing forms of MS (RRMS, CIS, SPMS) for the following higher-cost DMTs for MS: - Preferred branded products: now require PA and step therapy with a low-cost product. - Non-preferred branded products: modified step therapy to require a low-cost product and a higher-cost preferred brand product. • Clarification that Ocrevus (ocrelizumab) is also coverable under "particularly aggressive relapsing form of MS" criteria. • No changes to criteria or intent of Zeposia (ozanimod) for ulcerative colitis or Tysabri (natalizumab) for Crohn's disease.

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Medication Policy Manual **Policy No:** dru754

Topic: Elevidys**,** delandistrogene moxeparvovec **Date of Origin:** July 1, 2023

Committee Approval Date: September 19, 2024 **Next Review Date:** 2025

Effective Date: December 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Elevidys (delandistrogene moxeparvovec) is an intravenous medication that has received approval from the FDA to treat Duchenne muscular dystrophy (DMD). A clinical benefit, such as improved ambulation, from Elevidys (delandistrogene moxeparvovec) treatment has yet to be established.

Policy/Criteria

Most contracts require pre-authorization approval of Elevidys (delandistrogene moxeparvovec) prior to coverage.

I. Continuation of therapy (COT): Elevidys (delandistrogene moxeparvovec) is considered investigational for all conditions, per the full policy criteria below.

Please note: *Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Elevidys (delandistrogene moxeparvovec) is considered investigational for all conditions, including Duchenne muscular dystrophy (DMD). In addition, the use of Elevidys (delandistrogene moxeparvovec) in combination with any exon skipping therapy for DMD (e.g., Amondys 45 [casimersen], Exondys 51 [eteplirsen], Vyondys 53 [golodirsen], and Viltepso [viltolarsen]) is also considered investigational.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Elevidys (delandistrogene moxeparvovec) coverable under the medical benefit (as a provider administered medication).

B. Although the use of Elevidys (delandistrogene moxeparvovec) for Duchenne muscular dystrophy is considered investigational, if pre-authorization is approved, Elevidys (delandistrogene moxeparvovec) will be authorized in quantities of a one treatment course per lifetime.

C. Additional infusions of Elevidys (delandistrogene moxeparvovec) will not be authorized.

Position Statement

Summary

- Elevidys (delandistrogene moxeparvovec) is a novel, intravenous gene therapy that is delivered into the skeletal muscle cells via an adeno-associated viral vector, promoted to selectively express the transgene, producing a micro version of dystrophin (SRP-9001).
- Elevidys (delandistrogene moxeparvovec) was initially approved for the treatment of Duchenne muscular dystrophy (DMD), under the FDA Accelerated Approval Program based on an increase in micro-dystrophin (SRP-9001), expressed in skeletal muscles observed in patients during phase I and II trials. Subsequently, it has received full approval based on results of a phase III trial.
- A clinical benefit (e.g., prolongation of independent ambulation, improved quality of life, or prevention of disease progression and disability) of Elevidys (delandistrogene moxeparvovec) has not been established.
    * In two small trials (Study 102 and ENDEAVOR), Elevidys (delandistrogene moxeparvovec) was shown to increase micro-dystrophin (SRP-9001) levels. However, it has not yet been proven that an increase in micro-dystrophin will translate to improved clinical outcomes, such as improved motor function.
    * The two trials reported conflicting results in functional assessment score improvement: The primary endpoint of study 102 reported no significant difference between the group treated with Elevidys (delandistrogene moxeparvovec) and placebo; while ENDEAVOR, a single arm open label trial, reported exploratory endpoints with small improvements in functional assessments compared to an external control, however the clinical relevance of the improvement is unclear as the change did not meet the defined minimal clinically important differences.
    * A confirmatory phase 3 trial of Elevidys (delandistrogene moxeparvovec) has recently failed to meet significance in the primary endpoint of change in functional assessment score from baseline when compared to placebo, and the secondary endpoints of other functional assessments failed to meet the defined minimal clinically important differences, leading to further uncertainty of a clinical benefit.
    * Safety of use in specific exon mutations is a concern, as each trial submitted to the FDA has included different exon mutation criteria, with at least one serious adverse event being reported due to use in a specific exon mutation group. The ongoing phase 3 trial is using different exon mutation criteria than current submitted trials to FDA.
    * Given the lack of overall clinical benefit and potential safety concerns, the use of Elevidys (delandistrogene moxeparvovec) for DMD is considered investigational.
- The U.S. Centers for Disease Control and Prevention (CDC) has developed general management guidelines for DMD. The CDC recommends corticosteroids and supportive care to slow disease progression. These guidelines were published prior to the submission of Elevidys (delandistrogene moxeparvovec) to the FDA, thus the use of Elevidys (delandistrogene moxeparvovec) for DMD has not yet been addressed.[1-3]

Clinical Efficacy[4-10]

- The safety and efficacy of Elevidys (delandistrogene moxeparvovec) for FDA accelerated approval was established on a two small trials, one being a phase 2 multicenter, randomized, double-blind, placebo-controlled, parallel group trial (Study 102, n=41) and the second, a phase 1b single arm, open label, 4 cohort trial (ENDEAVOR, n=38), in which only cohort 1 (n=20) has reported to date.
- Patients in both trials were ≥ 4 or <8 years of age, had genetically confirmed DMD, considered ambulatory (defined as a North Star Ambulatory Assessment [NSAA] score between 13-26), on a consist steroid dose for at least 12 weeks, and negative for antibodies to the adeno associated viral vector.
- Concurrent use of exon skipping therapies such as Amondys 45 (casimersen), Exondys 51 (eteplirsen), Vyondys 53 (golodirsen), and Viltepso (viltolarsen) were excluded from the trials.
- The primary endpoint across for both trials was the change from baseline at 12 weeks of the percent of micro-dystrophin (SRP-9001) expressed.
    * Study 102: Using the clinically available Elevidys (delandistrogene moxeparvovec) compared to placebo, the change from baseline in micro-dystrophin (SRP-9001) expressed at 12 weeks was statistically significant (23.8%, p<0.0001) compared to placebo (not reported), however the second primary endpoint of change from baseline in NSAA at 48 weeks was not significant (+1.7 vs +0.9).
    * ENDEAVOR: Using the commercially available Elevidys (delandistrogene moxeparvovec) with no competitor arm, a significant improvement in the change from baseline in micro-dystrophin (SRP-9001) expressed was shown at 12 weeks (54.2%) in cohort 1 (n=20).
- Both studies demonstrated significant improvements in micro-dystrophin (SRP-9001) expression at 12 weeks after treatment via Western blot testing; however, the effect of increasing micro-dystrophin (SRP-9001) levels on clinical outcomes has not yet been established. There have been many trials in drugs (exon skipping therapies) in which the treatment arm has shown small improvements in dystrophin, but none of those trials to date have proven a correlation of improving dystrophin levels to clinically relevant outcomes.
- The evidence regarding the effect of Elevidys (delandistrogene moxeparvovec) based on the change from baseline on the NSAA score is inconclusive. The NSAA is a functional assessment of ambulatory DMD patients used primarily in clinical trials. Lower scores suggest greater disease severity and lower ambulatory ability; a minimal clinically important difference (MCID) is estimated to be an improvement of 3.5 points. The clinical relevance of the effect that Elevidys (delandistrogene moxeparvovec) showed (improvement of +0.8 in Study 102) is unclear at this time as it falls below the MCID and was not statistically significant.
- Recent topline results from the confirmatory EMBARK (n=125) trial, a phase 3, global, multicenter, double-blind, placebo-controlled study also failed to meet the primary endpoint of change from baseline in the NSAA score, with an improvement of +0.7 when

compared to placebo at 52 weeks (+2.6 vs +1.9), again falling below the MCID and not meeting statistical significance.

- Secondary and exploratory endpoints from these three trials and a proof-of-concept trial have also reported minimal improvements in NSAA and other timed function tests, however the improvements are below the MCID for these tests and are over a short duration for a small sample size, leading to further uncertainty of a meaningful benefit.
- Although the existing evidence is promising, additional confirmatory trials are needed to establish the safety and efficacy of Elevidys (delandistrogene moxeparvovec). Elevidys (delandistrogene moxeparvovec) has not yet proven to improve any clinically relevant outcomes such as prolongation of independent ambulation or quality of life, nor has it proven prevention of disease progression, disability, or mortality.
- At this time, there is not enough data available to determine that the benefits of Elevidys (delandistrogene moxeparvovec) use would provide any meaningful benefit in DMD.

Investigational Uses[4 5]

- Elevidys (delandistrogene moxeparvovec) is considered investigational when used in combination with other exon skipping therapies for DMD, including Amondys 45 (casimersen), Exondys 51 (eteplirsen), Vyondys 53 (golodirsen), and Viltepso (viltolarsen), as concurrent use in the trials submitted to the FDA was not allowed.

Safety[4 5 11]

- Limited safety data is available, however, the most common adverse reactions reported with Elevidys (delandistrogene moxeparvovec) during phase I/II trials included vomiting, and decreased appetite. Safety data for the ongoing phase III trial has yet to be published.
- Use of Elevidys (delandistrogene moxeparvovec) in specific exon mutations is unproven, as each trial submitted to the FDA has included different exon mutation criteria, with at least one serious adverse event (immune myositis) being reported due to use in a specific exon mutation group (exon mutations 1-17), and the ongoing phase 3 trial using different exon mutation criteria than current submitted trials to FDA.

Cross References
BlueCross BlueShield Association Medical Policy, 5.01.27 - Treatment for Duchenne Muscular Dystrophy [June 2023]
BlueCross BlueShield Association Medical Policy, Gene Therapies for Duchenne Muscular Dystrophy [October 2023]
Amondys 45, casimersen, Medication Policy Manual, Policy No. dru661
Exondys 51, eteplirsen, Medication Policy Manual, Policy No. dru480
Vyondys 53, golodirsen, Medication Policy Manual, Policy No. dru606
Viltepso, viltolarsen, Medication Policy Manual, Policy No. dru640

Codes	Number	Description
HCPCS	J1413	Injection, delandistrogene moxeparvovec, (Elevidys) $1.33x10^{14}$ vg/kg
ICD-10	G71.0	Muscular dystrophy

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9. Elevidys® [Prescribing Information]. Cambridge, MA: Sarepta; June 2024

10. Sarepta Pharmaceuticals I. Sarepta Therapeutics Announces Topline Results from EMBARK, a Global Pivotal Study of ELEVIDYS Gene Therapy for Duchenne Muscular Dystrophy, Press Release 2023. https://investorrelations.sarepta.com/static-files/4871976b-aebc-4ab1-b598-b9ad15c660bf

11. Proud CM, et al., Title: Integrated analyses of data from clinical trials of delandistrogene moxeparvovec in DMD, poster presentation, Accessed: 4/19/2023 https://investorrelations.sarepta.com/static-files/f71ee02c-3870-443f-a806-e12e44bae206

Revision History

Revision Date	Revision Summary
9/19/2024	Updated policy to reflect FDA full approval, with no change to intent.
12/7/2023	Updated policy to include new trial data, with no change to intent.
9/14/2023	Updated policy to reflect new brand name of Elevidys (delandistrogene moxeparvovec) in line with its FDA accelerated approval. No changes to criteria.
6/15/2023	New policy. Effective 7/15/2023. Use of delandistrogene moxeparvovec is considered investigational in the treatment of all conditions, including Duchenne muscular dystrophy (DMD). In addition, use of delandistrogene moxeparvovec in combination with any exon skipping therapy for DMD is considered investigational.

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Medication Policy Manual | **Policy No:** dru761

Topic: Bispecific T-Cell Engager (BiTE) Therapies for B-Cell Lymphoma

- Columvi, glofitamab-gxbm
- Epkinly, epcoritamab-bysp
- Lunsumio, mosunetuzumab-axgb

Date of Origin: October 15, 2023

Committee Approval Date: March 6, 2025 | **Next Review Date:** 2026

Effective Date: May 1, 2025

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

The medications in this policy are provider-administered intravenous bispecific T-cell engager (BiTE) medications used in the treatment of specific types of B-cell lymphoma. They help the immune system (T-cells) recognize and destroy B-cells that express the CD20 antigen.

Policy/Criteria

Most contracts require pre-authorization approval of bispecific T-cell engager (BiTE) therapies for B-cell lymphoma [as listed in *Table 1*] prior to coverage.

I. Continuation of therapy (COT): Bispecific T-cell engager (BiTE) therapies for B-cell lymphoma may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.

II. New starts (treatment-naïve patients): Bispecific T-cell engager (BiTE) therapies for B-cell lymphoma may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that the applicable diagnosis-based criteria below are met (refer to *Table 1*).

Table1:

Diagnosis	Coverable Medications	ALL of the following diagnostic criteria are met:
Diffuse large B-cell lymphoma, not otherwise specified (DLBCL NOS) *Note: Includes DLBCL arising from indolent lymphoma*	- Epkinly (epcoritamab) - Columvi (glofitamab)	**1.** A diagnosis of CD20-positive DLBCL NOS. **2.** Documented disease progression on or after at least two prior systemic lymphoma therapies, including a CD20-directed monoclonal antibody (e.g., rituximab). **3.** Will be used as monotherapy. **4.** No prior use of CD20-directed BiTE therapy [as listed in *Table 1*]. **5.** **For Columvi (glofitamab) only***:* Columvi (glofitamab) will be preceded by an initial dose of Gazyva (obinutuzumab).
Follicular lymphoma (FL)	- Epkinly (epcoritamab) - Lunsumio (mosunetuzumab)	**1.** A diagnosis of follicular lymphoma (FL), **2.** The FL is Grade 1-2, or 3a. **3.** The FL relapsed after or was refractory to at least two prior systemic therapies which must have included each of the following (a and b): a. An anti-CD20-directed monoclonal antibody (see *Appendix A*). b. An alkylating agent (see *Appendix B*) or lenalidomide (generic Revlimid). **4.** Will be given as monotherapy. **5.** No prior use of CD20-directed BiTE therapy [as listed in *Table 1*].
High-grade B-cell lymphoma (HGBCL)	Epkinly (epcoritamab)	**1.** A diagnosis of CD20-positive HGBCL. **2.** Documented disease progression on or after at least two prior systemic lymphoma therapies, including a CD20-directed monoclonal antibody (e.g., rituximab). **3.** Will be used as monotherapy. **4.** No prior use of CD20-directed BiTE therapy [as listed in *Table 1*].

Large B-cell lymphoma arising from follicular lymphoma (FL)	Columvi (glofitamab)	**1.** A diagnosis of CD20-positive large B-cell lymphoma arising from FL. **2.** Documented disease progression on or after at least two prior systemic lymphoma therapies, including a CD20-directed monoclonal antibody (e.g., rituximab). **3.** Will be used as monotherapy. **4.** Columvi (glofitamab) will be preceded by an initial dose of Gazyva (obinutuzumab). **5.** No prior use of CD20-directed BiTE therapy [as listed in *Table 1*].

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers BiTE therapies for B-cell lymphoma coverable only under the medical benefit (as provider-administered medications).

B. When pre-authorization is approved, BiTE therapies for B-cell lymphoma may be authorized as follows:

Table 2. Quantity Limitations and Authorization Period

Product	Quantity Limit
Columvi (glofitamab)	Up to FDA-recommended dose and frequency limits for a maximum of 13 infusions. No additional quantities will be authorized. **Initial authorization:** 9 infusions in 24 weeks (cycles 1-8) **One-time reauthorization**: 4 infusions in 12 weeks (cycle 9-12)
Epkinly (epcoritamab)	Up to FDA-recommended dose and frequency limits until disease progression, as follows: [a] **Initial authorization:** 18 infusions in 24 weeks (cycles 1 to 6). **Initial re-authorization**: 9 infusions in 24 weeks (cycles 7 to 12). **Subsequent re-authorizations**: six infusions in 24 weeks ongoing (cycle 13 and beyond). [a] See *Table 3* for additional details regarding dosing.
Lunsumio (mosunetuzumab)	Up to FDA-recommended dose and frequency limits until disease progression, as follows: [b] **Initial authorization:** 10 infusions in 24 weeks (cycles 1 to 8). [b] **Additional authorization (up to one-time)**: [b] **1.** *For complete response*: If a complete response is achieved after the initial eight cycles of Lunsumio (mosunetuzumab), no additional cycles will be authorized.

	2. *For partial response or stable disease*: **a.** If a partial response or stable disease is achieved after the initial eight cycles of Lunsumio (mosunetuzumab), up to nine additional 21-day cycles may be authorized. **b.** No additional Lunsumio (mosunetuzumab) will be authorized (17 cycles in total).

[b] See *Table 4* for additional details regarding dosing.

C. Reauthorization: Authorization **shall** be reviewed at least every 24 weeks for documented benefit (not to exceed the maximum Quantity Limit in *Table 2* above). Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met. Specifically, documentation that the medication is providing clinical benefit, including disease stability or improvement, and lack of disease progression, based on an assessment of change in tumor burden. If there is documentation of potential disease progression, a shortened authorization (up to three months) may be approved to allow time for clarification of response to BiTE therapy, including clinical re-evaluation of the patient and reimaging.

PLEASE NOTE: Additional doses of BiTE therapy will not be authorized without a documented recent assessment by the treating provider (such as oncologist) with objective evidence of response to therapy, such as by re-imaging and use of RECIST v1.1 (modified RECIST) and/or Lugano criteria.

IV. BiTE therapies for B-cell lymphoma are considered investigational when used for all other conditions not listed in the coverage criteria above (*Table 1*), as well as

A. Epkinly (epcoritamab) or Lunsumio (mosunetuzumab): Grade 3b follicular lymphoma (FL)

Position Statement

Summary

- The bispecific T-cell engager (BiTE) therapies for B-cell lymphoma help the immune system (T-cells) recognize and destroy lymphoma cells and healthy B-lineage cells that express the CD20 antigen.
- The currently approved BiTE therapy products for B-cell lymphoma include the following:
  - Columvi (glofitamab), approved for use in DLBCL NOS and large B-cell lymphoma arising from follicular lymphoma (FL) after two or more prior lines of systemic therapy.
  - Epkinly (epcoritamab), approved for use in:

    - Diffuse large B-cell lymphoma (DLBCL) not otherwise specified (NOS) and high-grade B-cell lymphoma (HGBCL) after two or more prior lines of systemic therapy.
    - Follicular lymphoma, after two or more prior lines of systemic therapy.

  * Lunsumio (mosunetuzumab), approved for use in FL after at least two prior lines of systemic therapy, including an alkylating agent and an anti-CD20-directed monoclonal antibody.

- The intent of this policy is to allow coverage of BiTE therapies for B-cell lymphoma in the settings described above (in the coverage criteria), where they have been evaluated for efficacy, up to the doses shown to be safe in clinical trials.
- The FDA approvals were based on poor quality evidence from small, non-comparative, non-blinded studies that evaluated tumor response, a surrogate endpoint. Though tumor responses in the studies were quite high, it is not yet known if they will be durable and will translate into improved overall survival, the clinical outcome of interest.
- The patients enrolled in the studies evaluating the BiTE therapies in B-cell lymphoma had a median of three prior therapies for B-cell lymphoma. All had prior therapy with anti-CD20 monoclonal antibodies (e.g., rituximab) and anthracyclines. The populations included patients who may have had prior autologous hematopoietic stem cell transplant (HSCT) or chimeric antigen receptor T-cell (CAR T) therapy.
- It is not known how the BiTE therapies compare with other B-cell lymphoma therapies. Optimal sequencing of therapies in the subsequent-line treatment of B-cell lymphoma is also not known.
- The National Comprehensive Cancer Network (NCCN) B-cell lymphomas guideline lists the BiTE therapies for B-cell lymphoma among therapy options in the third- and subsequent-line treatment setting in the subpopulations in which they are indicated.
- The BiTE therapies for B-cell lymphoma are administered as monotherapy. Their safety and efficacy have not been established when used in combination with other therapies.
- The BiTE therapies for B-cell lymphoma must be given by trained providers who have access to facilities that have the means to effectively manage the serious adverse effects (AEs) that are associated with their administration. Package labeling indicates that both therapies need to be initiated in an inpatient setting.
- The BiTE therapies for B-cell lymphoma may cause serious AEs including cytokine release syndrome (CRS) and serious neurological toxicities which can be life threatening. Columvi (glofitamab) is preceded by a single dose of Gazyva (obinutuzumab) to deplete circulating and lymphoid tissue B cells to reduce the incidence and severity of CRS. The use of other anti-CD20 monoclonal antibodies has not been studied in this setting.
- *Reauthorization Criteria*: When coverage criteria are met, BiTE therapies (as listed in *Table 1*) are authorized for six months (24 weeks) of therapy, after which time documentation must be provided to establish that the medication is effective (or as specified in *Table 2. Quantity Limit*). Specifically, there must be documentation of clinical benefit, including disease stability or improvement and there is a lack of disease progression, based on an assessment of change in tumor burden. Documentation of

benefit must include an assessment of the most recent imaging ("restaging scans") and/or re-biopsy by the treating oncologist.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Clinical Efficacy

Background

- The bispecific T-cell engager (BiTE) therapies for B-cell lymphoma currently include Epkinly (epcoritamab), Columvi (glofitamab), and Lunsumio (mosunetuzumab).
- They target the CD20 antigen on B-cells.
- They bind to the CD3 receptor on T-cells and the CD20 antigen expressed on the surface of lymphoma cells thus initiating a T-cell -mediated immune response.

Diffuse large B-cell lymphoma (DLBCL), High-Grade B-cell lymphoma (HGBCL), and large B-cell lymphoma (LBCL)

Each received initial FDA Accelerated approval in their respective diffuse large B-cell lymphoma (DLBCL) populations based on small, single-arm, non-blinded trials that evaluated tumor response, an unvalidated surrogate endpoint, as the primary endpoint. The evidence is of poor quality. Confirmatory trials are required to confirm clinical benefit. [1,2]

- **Epkinly (epcoritamab)** was approved for DLBCL not otherwise specified (NOS), including DLBCL arising from indolent lymphoma (e.g., marginal zone lymphoma), and for high-grade B-cell lymphoma (HGBCL) after two or more lines of systemic therapy based on evidence from study GCT3013-01 (EPCORE NHL-1). [3]

    * The study (N=148) enrolled patients with CD20-positive DLBCL NOS (86%) and HGBCL (14%) who had a median of 3 prior therapies for their advanced disease. All had prior anti-CD20 monoclonal antibody (mAb) therapy, an alkylating agent, and an anthracycline.
    * Eighteen percent of the population had a prior autologous hematopoietic stem cell transplant (HSCT) and 39% had prior chimeric antigen receptor T-cell (CAR T) therapy.
    * Patients with CNS lymphoma or prior allogeneic HSCT were not allowed to participate in the study.
    * The overall response rate (ORR) was 61% and the complete response (CR) rate was 38%. The median duration of response (DOR) was 15.6 months.
- **Columvi (glofitamab)** was approved for DLBCL NOS, and large B-cell lymphoma (LBCL) arising from follicular lymphoma (FL) after two or more lines of systemic therapy based on evidence from study NP31079. [4]
    * The study (N=132) enrolled patients with CD20-positive DLBCL NOS (80%) and LBCL arising from FL (20%) who had a median of 3 prior therapies for their advanced disease. All had prior anti-CD20 mAb therapy.
    * Nineteen percent of the population had a prior autologous HSCT and 30% had prior CAR T therapy.
    * Patients with CNS lymphoma or prior allogeneic HSCT were not allowed to participate in the study.
    * The ORR was 56% and the CR rate was 43%. The median DOR was 18.4 months.
- It is not known how the efficacy of BiTE therapies for B-cell lymphoma compares with any other therapy for B-cell lymphoma as no head-to-head studies have been conducted.
- The National Comprehensive Cancer Network (NCCN) B-cell lymphomas guideline lists either Epkinly (epcoritamab) or Columvi (glofitamab) among potential therapies for DLBCL when there has been disease progression on or after at least two prior systemic therapies. Epkinly (epcoritamab) is also listed as an option for transformed FL or marginal zone lymphoma (MZL), and HGBCL. Columvi (glofitamab) is also listed as an option for transformed FL or nodal MZL. [5]

Follicular lymphoma (FL)

- Follicular lymphoma (FL) is the second most common non-Hodgkin lymphoma (NHL).
- The World Health Organization (WHO) classifies FL using several Grades (FL1-2, FL3A, FL3B) based on the number of centroblasts that are present to stratify patients based on expected outcomes. Grade 3B FL is also known as 'transformed FL' and is generally treated using therapy pathways for diffuse large B-cell lymphoma (DLBCL). [5]
- Both Lunsumio (mosunetuzumab) and Epkinly (epcoritamab) received initial FDA Accelerated approval in their respective follicular lymphoma (FL) populations based on small, single-arm, non-blinded trials that evaluated tumor response, an unvalidated surrogate endpoint, as the primary endpoint. The evidence is of poor quality. Confirmatory trials are required to confirm clinical benefit. [1,6]

- **Lunsumio (mosunetuzumab)** received FDA accelerated approval based on a single-arm, open-label study in adults with Grades 1 to 3a relapsed or refractory FL that evaluated tumor response as the primary endpoint. [7,8]
    * Patients in the study relapsed after or failed to respond to at least two prior systemic therapies (median of 3).
        - All patients had a prior alkylating agent and a prior anti-CD20-directed monoclonal antibody.
        - Three percent of patients had a prior chimeric antigen receptor (CAR) T-cell therapy for their FL.
    * Patients with prior allogeneic stem cell transplant (SCT) were excluded from participating in the study due to the high likelihood of severe immune reactions; however, 21% of the population had a prior autologous SCT.
    * The objective response rate (ORR) was 80% with 60% being complete responses. The median duration of response was 22.8 months.
    * Though the reported ORRs were very high in this study, it is not yet known how durable the responses will be, or whether Lunsumio (mosunetuzumab) will ultimately improve overall survival, the clinical outcome of interest.
- **Epkinly (epcoritamab)** received FDA accelerated approval based on a phase 2 cohort of the single-arm, open-label study [EPCORE NHL-1 (Study GCT3013-01)] (n=128). The cohort included adults with relapsed or refractory CD20+ FL, (Grades 1 to 3a) and evaluated tumor response as the primary endpoint.[9]
    * Patients in the study relapsed after or failed to respond to at least two prior systemic therapies [median of 3 (2-4)].
        - All patients had a prior anti-CD20-directed monoclonal antibody and either prior alkylating agent or lenalidomide. Although alkylating agent use was not required for enrollment in the trial, 100% of patients had prior alkylating agent. Thirty-one percent of patients had prior lenalidomide (21% lenalidomide with anti-CD20 rituximab).
        - Five percent of patients had a prior chimeric antigen receptor (CAR) T-cell therapy for their FL.
    * Patients with prior allogeneic stem cell transplant (SCT) were excluded from participating in the study due to the high likelihood of severe immune reactions; however, 19% of the population had a prior autologous SCT.
    * The objective response rate (ORR) was 82% with 62% being complete responses. More than 58.4% of responders remained in response at 18 months.
    * Though the reported ORRs were very high in this study, it is not yet known how durable the responses will be, or whether Epkinly (epcoritamab) will ultimately improve overall survival, the clinical outcome of interest.
- BiTE therapies for B-cell lymphoma [Lunsumio (mosunetuzumab) or Epkinly (epcoritamab)] have not been directly compared with any other therapy, including CAR T-cell therapies which also are associated with high ORRs.

- The National Comprehensive Cancer Network (NCCN) B-cell lymphomas guideline lists Lunsumio (mosunetuzumab) and Epkinly (epcoritamab) among potential systemic therapy options for relapsed or refractory FL (Grade 1-2) in the third- and subsequent-line treatment setting. The NCCN guideline notes that Grade 3B FL should be treated using the DLBCL pathway. [5]

Reauthorization Criteria:

When coverage criteria are met, BiTE therapies (as listed in *Table 1*) are authorized for six months (24 weeks) of therapy, after which time documentation must be provided to establish that the medication is effective. Specifically, there must be documentation of clinical benefit, including disease stability or improvement and there is a lack of disease progression, based on an assessment of change in tumor burden.

- The standard of care for evaluation of response to cancer therapy is use of the RECIST criteria for assessment of solid tumor burden and Lugano criteria for non-solid tumors, such as lymphoma, as well as iRECIST criteria for some cancer immunotherapy.[10-12] Criteria used for assessment of response vary, depending on the tumor type and the therapy. Pivotal trials of BiTE therapies for lymphoma used the following criteria, for assessment of tumor burden and response to therapy.
    * Lugano criteria.[12]
    * Lymphoma Response to Immunomodulatory Therapy Criteria (LYRIC) [modified Lugano][13]
    * RECIST v1.1 criteria (modified RECIST)[10]
- These criteria, include use of quantitative and qualitative criteria for assessment of change in tumor burden for target lesions and non-target lesions.
    * Quantitative measurements for target lesions (tumor size and % change)
    * Qualitative evaluation for non-target lesions (present/disappeared/ unequivocal progression)
- Documentation of benefit must include an assessment of the most recent imaging ("restaging scans") and/or re-biopsy by the treating oncologist. Given the complexity of the evaluation, including use of the modified RECIST and LYRIC criteria, BiTE therapies for lymphoma will not be reauthorized without an assessment of response to therapy, such a partial response (PR), complete response (CR), or stable disease (SD).
- Though not specific to the use of BiTE therapies for lymphoma, use of immunotherapy may result in pseudoprogression, due to immune and T-cell activation, which can appear similar to tumor flare. If there is documentation of potential disease progression ["unconfirmed progressive disease (UPD)"], a shortened authorization (up to three months) may be approved to allow time for clarification of response to BiTE therapies for lymphoma, including clinical re-evaluation of the patient and reimaging. Guidelines recommend reimaging for UPD after 4-8 weeks. Study protocols for BiTE therapies for lymphoma required reassessment (rescan) between 4 to 12 weeks.[14]
- If a patient has confirmed, unequivocal new lesions (progression of disease, PD), additional doses of BiTE therapies for lymphoma are not coverable. If a new lesion is equivocal, UPD reassessment by the treating oncologist, with repeat tumor assessment, with imaging and/or re-biopsy, would apply (as noted above).

Investigational Uses [15-17]

- There are ongoing studies evaluating the BiTE therapies in other types of B-cell lymphomas. However, benefit in the treatment of conditions other than the large B-cell lymphoma subtypes listed in the coverage criteria has not yet been established.
    * Lunsumio (mosunetuzumab) is currently only indicated as a monotherapy. Future studies are planned which combine it with other medications such as lenalidomide; however, the safety and efficacy of these combinations is not yet established.
    * Columvi (glofitamab) was evaluated in DLBCL NOS in the second- and subsequent-line setting where it was compared with chemotherapy (R-GemOx). Although the study reported an overall OS advantage with Columvi (glofitamab) it was largely driven by patients enrolled in Asia. In patients enrolled in European and N. American sites the OS advantage appeared to favor R-GemOx.
    * Columvi (glofitamab) is also being evaluated in mantle cell lymphoma (MCL); however, there are no comparative data or outcomes data to support a benefit in this setting.

Safety and Tolerability [1,2,6]

- All BiTE therapies for B-cell lymphoma have a Box Warning describing the risk of cytokine release syndrome (CRS). Epkinly (epcoritamab) and Lunsumio (mosunetuzumab) have an additional Box Warning for immune effector cell-associated neurotoxicity (ICANS). Like CAR T-cell therapies, BiTE therapies for B-cell lymphoma should only be administered by qualified healthcare professionals with experience and appropriate medical support to manage these toxicities.
- The most common serious adverse events associated with the BiTE therapies for B-cell lymphoma include cytokine release syndrome (CRS), sepsis, fever and neutropenia, and tumor flare.
- In clinical trials, tocilizumab (Actemra) (+/- corticosteroids) was used for management of CRS.

Dosing and Administration [1,2,6]

- The BiTE therapies for B-cell lymphoma require hospitalization when therapy is initiated.
- Epkinly (epcoritamab) is administered via subcutaneous injection. Columvi (glofitamab) is given via intravenous infusion over two to four hours.
- <u>For Columvi (glofitamab) – DLBCL and Large B-cell lymphoma arising from FL</u>:
    * Given for a maximum of 12 cycles [cycles are 21 days each]
    * Cycle 1 consists of two test infusions (“step up dose 1” and “test dose 2”), followed by 11 maintenance doses, given once every 21-day cycle.
    * A single infusion of Gazyva (obinutuzumab) is given prior to initiating therapy with Columvi (glofitamab) to deplete circulating and lymphoid tissue B cells to reduce the incidence and severity of CRS.

- For Epkinly (epcoritamab) for DLBCL, HGBCL, and FL:
  * Cycle 1:
    - For DLBCL and HGBCL: Cycle 1 consists of two test infusions ("step up dose 1" and "step up dose 2"), followed by two maintenance doses, to complete the first 28-day cycle. For FL: Cycle 1 consists of three test infusions ("step up dose 1," "step up dose 2," and "step up dose 3"), followed by one maintenance dose, to complete the first 28-day cycle.
  * Cycle 2 and 3: four doses in each 28-day cycle.
  * Cycles 4 to 9: two doses per 28-day cycle.
  * Cycles 10 and beyond: one dose per 28-day cycle

Table 3. Epkinly doses per cycle -DLBCL, HGBCL, and FL [a]

	Doses per cycle		**Doses per cycle**
Cycle 1	4 doses	**Cycle 7**	2 doses
Cycle 2	4 doses	**Cycle 8**	2 doses
Cycle 3	4 doses	**Cycle 9**	2 doses
Cycle 4	2 doses	**Cycle 10**	1 dose
Cycle 5	2 doses	**Cycle 11**	1 dose
Cycle 6	2 doses	**Cycle 12**	1 dose
Authorization #1	**18 doses**	**Authorization #2**	**9 doses**

[a] Authorization #3 (and beyond): six doses per 24 weeks.

- For Lunsumio (mosunetuzumab) for FL:
  * Given on Day 1 of each 21-day cycle.
  * Cycle 1 consists of two test infusions ("step up dose 1" on day 1 and "test dose 2" on day 8), followed by one maintenance dose, to complete the first 21-day cycle.
  * Cycles 2 to 8: one dose per 21-day cycle.
  * Lunsumio (mosunetuzumab) is given for an initial 8 cycles at which point response to therapy is assessed.
    - If the patient has a complete response to therapy, no additional medication is given.
    - If there is a partial response or stable disease, up to nine additional cycles (Cycles 9 to 17) of Lunsumio (mosunetuzumab) may be administered (total of 17 cycles).
  * Refer to the Lunsumio (mosunetuzumab) prescribing information for the specific information regarding dose, dosing intervals, and infusion times.

Table 4. Lunsumio (mosunetuzumab**) doses per cycle - FL**

	Doses per cycle		**Doses per cycle**
Cycle 1	3 doses	**Cycle 9**	1 dose
Cycle 2	1 dose	**Cycle 10**	1 dose
Cycle 3	1 dose	**Cycle 11**	1 dose
Cycle 4	1 dose	**Cycle 12**	1 dose
Cycle 5	1 dose	**Cycle 13**	1 dose
Cycle 6	1 dose	**Cycle 14**	1 dose
Cycle 7	1 dose	**Cycle 15**	1 dose
Cycle 8	1 dose	**Cycle 16**	1 dose
		Cycle 17	1 dose
Authorization #1	**10 doses**	**Authorization #2**	**9 doses**

Appendix A: Anti-CD20-Directed Monoclonal Antibodies Used in the Treatment of FL
Obinutuzumab (Gazyva)
Rituximab (biosimilars, Rituxan)

Appendix B: Alkylating Agents Used in the Treatment of Follicular Lymphoma (FL)
Bendamustine (generic Treanda)
Chlorambucil (generic Leukeran)
Cyclophosphamide (generic Cytoxan)

Cross References
Bruton's tyrosine kinase (BTK) inhibitors, Medication Policy Manual, Policy No. dru691
Chimeric Antigen Receptor (CAR) T-cell Therapies, Medication Policy Manual, Policy No. dru523
Gazyva, obinutuzumab, Medication Policy Manual, Policy No. dru327
Monjuvi, tafasitamab, Medication Policy Manual, Policy No. dru652
PI3K Inhibitors, Medication Policy Manual Policy No. dru706
Polivy, polatuzumab vedotin, Medication Policy Manual, Policy No. dru600
Products with Therapeutically Equivalent Biosimilars/Reference Products, Medication Policy Manual, Policy No. dru620
Tazverik, tazemetostat, Medication Policy Manual Policy No. dru627
Xpovio, selinexor, Medication Policy Manual, Policy No. dru607
Zynlonta, loncastuximab tesirine, Medication Policy Manual, Policy No. dru675

Codes	Number	Description
HCPCS	J9321	Injection, epcoritamab (Epkinly), 0.16 mg
HCPCS	J9286	Injection, glofitamab (Columvi), 2.5 mg
HCPCS	J9350	Injection, mosunetuzumab-axgb, 1 mg

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Revision History

Revision Date	Revision Summary
3/6/2025	No changes to coverage criteria with this annual review.
12/12/2024	**Effective 1/15/2025:** • Add coverage for Epkinly (epcoritamab) for relapsed or refractory follicular lymphoma (new indication). • Add Lunsumio, mosunetuzumab-axgb, another BiTE for B-cell lymphoma (archive dru745) and modified criteria to align with Epkinly (epcoritamab), for administrative purposes (no change to intent).
9/19/2024	**Effective 1/1/2025:** • Changed all approvals from every 12 months to every 24 weeks (six months). Ongoing therapy (beyond 24 weeks) will be subject to reauthorization review every 24 weeks, for documentation of disease stability or improvement and lack of disease progression. Update Quantity Limits to align with authorization periods. • Added additional clarification for Columvi (glofitamab) surrounding authorization limits stating coverage will be provided for up to 12 months or until disease progression (as per FDA-approved dosing).
3/21/2024	Added additional clarification for Columvi (glofitamab) surrounding authorization limits stating coverage will be provided for up to 12 months or until disease progression (as per FDA-approved dosing).
12/7/2023	Updated Epkinly (epcoritamab) continued authorization criteria to include the language "until disease progression" for consistency across other oncology policies.
9/14/2023	New policy (effective 10/15/2023). • Limits coverage of BiTE therapies for diffuse large B-cell lymphoma (DLBCL) when used as monotherapy as follows: - ***Epkinly (epcoritamab):*** Coverable for CD20-positive, relapsed or refractory DLBCL not otherwise specified (NOS) [including DLBCL arising from low-grade lymphoma] and high-grade B-cell lymphoma (HGBCL) when disease has progressed on or after at least two prior systemic lymphoma therapies. - ***Columvi (glofitamab):*** Coverable for CD20-positive relapsed or refractory DLBCL NOS, or large B-cell lymphoma (LBCL) arising from follicular lymphoma (FL) when disease has progressed on or after at least two prior systemic lymphoma therapies. • Sequential use of BiTE therapies for DLBCL has not been studied or shown to be effective and is therefore not coverable.

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Medication Policy Manual | **Policy No:** dru762

Topic: Complement Inhibitors for the Eye | **Date of Origin:** July 15, 2024

- Izervay, avacincaptad pegol
- Syfovre, pegcetacoplan

Committee Approval Date: June 20, 2024 | **Next Review Date:** 2024

Effective Date: July 15, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Syfovre (pegcetacoplan) and Izervay (avacincaptad pegol) are intravitreal (directly into the eye) complement inhibitors used for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

Policy/Criteria

Most contracts require pre-authorization approval of Complement Inhibitors for the Eye (as listed in Table 1) prior to coverage.

I. Continuation of therapy (COT): Complement Inhibitors for the Eye (as listed in Table 1) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, full policy criteria must be met for coverage.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Complement Inhibitors for the Eye (as listed in *Table 1*) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) confirming that criteria A and B below are met:

A. A diagnosis of **geographic atrophy (GA) secondary to age-related macular degeneration (AMD) only** has been established by a specialist in ophthalmology.

AND

B. **For Izervay (avacincaptad pegol) only:** There is clinical documentation (including, but not limited to chart notes) that the GA secondary to AMD is located outside of the foveal center (see *Appendix 1* for terminology).

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Complement Inhibitors for the Eye (as listed in *Table 1*) coverable only under the medical benefit (as provider-administered medications).

B. When pre-authorization is approved, Complement Inhibitors for the Eye will be authorized for 12 months, in quantities outlined in *Table 1*.

TABLE 1. Complement Inhibitors for the Eye

Product	Quantity Limit			
Syfovre (pegcetacoplan) 15mg (0.1ml of 150mg/ml solution)	Single eye treated		Both eyes treated	
	Monthly injection	Every Other Month injection	Monthly injection	Every Other Month injection
	1 vial per 25 days	1 vial per 60 days	2 vials per 25 days	2 vials per 60 days
Izervay (avacincaptad pegol) 2mg (0.1ml of 20mg/ml solution)	Single eye treated Monthly injection		Both eyes treated Monthly injection	
	1 vial per 28 days		2 vials per 28 days	

C. Continued Authorization:

a. **For Syfovre (pegcetacoplan) only**: Authorization **shall** be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement, such as a reduction in progression of geographic atrophy lesion area size relative to baseline.

b. **For Izervay (avacincaptad pegol) only**: No continued authorization will be granted after a one-year total duration of therapy, per the current prescribing information for Izervay (avacincaptad pegol).

IV. Complement Inhibitors for the Eye (as listed in Table 1) are considered investigational when used for all other conditions, including but not limited to:

A. Geographic atrophy secondary to Stargardt disease

B. Geographic atrophy secondary to cone rod dystrophy

C. Geographic atrophy secondary to toxic maculopathies

D. Geographic atrophy secondary to ANY condition OTHER THAN age-related macular degeneration (AMD).

Position Statement

Summary

- The intent of this policy is to allow coverage for Complement Inhibitors for the Eye (as listed in Table 1) for the treatment of geographic atrophy secondary to age-related macular degeneration, when the diagnosis has been established by a specialist in ophthalmology, up to the doses shown to be safe and effective in clinical trials.
- Syfovre (pegcetacoplan), a C3 protein complement inhibitor, was evaluated in two phase 3 trials (OAKS and DERBY) and found to reduce GA lesion growth with either monthly or every other month injections. The trials evaluated a *broad* geographic atrophy (GA) population, involving patients with ***both*** extrafoveal (GA lesion border more than 1 micrometer from foveal center point) and foveal (GA lesion present at the center point of fovea) geographic atrophy secondary to age-related macular degeneration (AMD). [1 2]
- Izervay (avacincaptad pegol),a C5 protein complement inhibitor, was evaluated in two, phase 3 trials and found to reduce GA lesion growth with monthly injections. These two trials evaluated ***only*** subjects with non-foveal (see *Appendix 1*) geographic atrophy secondary to age-related macular degeneration. [3-6]
- Pivotal trials had high rates of discontinuation and ocular adverse events, due to treatment being given by intravitreal administration.
- The safety and efficacy of Syfovre (pegcetacoplan) and Izervay (avacincaptad pegol) in the treatment of geographic atrophy secondary to any condition *other than* age-related macular degeneration (AMD) is unknown. Pivotal trials excluded subjects with geographic atrophy secondary to any other condition, other than age-related macular degeneration.
- In clinical trials, both Syfovre (pegcetacoplan) and Izervay (avacincaptad pegol) were associated with *new onset* neovascular (wet) AMD (nAMD), prompting additional treatment with vascular endothelial growth factor (VEGF) inhibitors.
- There are no head-to-head trials comparing Syfovre (pegcetacoplan) and Izervay (avacincaptad pegol) to one another.
- Complement Inhibitors for the Eye may be covered for the doses shown to be safe and effective in clinical trials.
- Izervay (avacincaptad pegol) may be covered for up to 1 year of treatment (per current prescribing information). The safety and effectiveness of higher, more frequent doses or treatment duration longer than 1 year have not been established.

Disease Background (see Appendix 1 for Terminology)

Geographic Atrophy (GA) Secondary to Age-related Macular Degeneration (AMD)

- Geographic atrophy is a late-stage (advanced) form of dry age-related macular degeneration characterized by the expansion of atrophic lesions in the outer retina which cause progressive and irreversible loss of photoreceptors, retinal pigment epithelium (RPE) and choriocapillaris (the dense network of capillaries that nourishes the outer layers of the retina). Lesions often begin in the extrafoveal regions and expand

to the fovea (center of the macula where vision is the sharpest) later in the disease (median 2.5-year timeframe from non-foveal to foveal progression). [1 7 8]

- Several lesion characteristics determine the rate of GA progression: baseline GA lesion size (larger lesions progress faster), lesion focality (multifocal lesions have higher progression rates than unifocal lesions), lesion location (non-foveal lesions progress faster than foveal lesions), and bilateral GA (more rapid progression if present in both eyes). [7]
- The goal of treatment with complement inhibitors for the eye is preservation of functional retinal cells by reduction of lesion area size, thereby slowing progression of the disease.

Clinical Efficacy

Syfovre (pegcetacoplan)

- At 24 months, the OAKS and DERBY trials showed statistically significant results in favor of Syfovre (pegcetacoplan) compared to placebo for the reduction of lesion area size, in subjects ≥60 years old (mean 78 years of age), with unifocal and multifocal, foveal and non-foveal, predominantly bilateral geographic atrophy, without choroidal neovascularization (CNV) in the treated eye only (subjects could have CNV in the fellow eye, which is a risk factor for developing CNV in the treated eye) at baseline. [1 2 9]
- In the OAKS trial, at 24 months, treatment with Syfovre (pegcetacoplan) showed a 22% and 18% lesion area growth reduction in the monthly and every other month injection frequencies, respectively.[1]
- In the DERBY trial, at 24 months, treatment with Syfovre (pegcetacoplan) showed a 19% and 16% lesion area growth reduction in the monthly and every other month injection frequencies, respectively. [2]
- Between the two trials, efficacy was higher for Syfovre (pegcetacoplan) treatment with *monthly* injections, compared to every other month injections, however, overall adverse events were higher in the monthly injection cohort as well.
- Per literature report and expert feedback, the use of an anatomical endpoint (lesion area size reduction) is appropriate in GA given the significance of lesions in the progression of GA secondary to AMD. It is a reproducible endpoint with correlation to disease progression and severity.
- Epidemiological studies, literature reports and expert feedback have estimated that more than a 20% reduction in lesion area size would have clinical benefit in retinal tissue structure preservation, if not visual acuity
- In the OAKS and DERBY trials, no statistically significant difference was noted in the secondary endpoints that measured visual function, including best corrected visual acuity (BCVA). Per literature reports and expert feedback, BCVA often underrepresents functional deficits in geographic atrophy due to foveal sparing in some patients; there is not a strong correlation between BCVA changes and lesion size, and BCVA is a poor metric of visual function in geographic atrophy secondary to AMD. [1 2 10]

Izervay (avacincaptad pegol)

- At 12 months, the GATHER1 and GATHER2 trials showed statistically significant results in favor of Izervay (avacincaptad pegol) compared to placebo for the reduction of growth rate in lesion area size, in subjects ≥50 years old (mean age 78 years), with unifocal and multifocal lesions, *only non-foveal* lesions, predominantly bilateral geographic atrophy, without choroidal neovascularization in *either* eye (treated or fellow) at baseline. [3-6 11]
    * In GATHER1, at 12 months, the reduction in the mean GA growth rate was 27.4 % (p=0.0072) for the Izervay (avacincaptad pegol) 2 mg group compared to its corresponding sham-treated group.[3]
    * In GATHER2, at 12 months, the reduction in the mean GA growth rate was 14% (p=0.0064) for the Izervay (avacincaptad pegol) 2mg treatment group compared to the sham group. [6]
    * In the GATHER1 and GATHER 2 trials, no statistically significant difference was noted in the secondary endpoints that measured visual function, including best corrected visual acuity (BCVA). [3-6]
- Safety and efficacy data for the use of Izervay (avacincaptad pegol) in the treatment of GA secondary to AMD beyond 12 months is still pending and unpublished.

Investigational Uses

There is insufficient evidence to establish the efficacy of Syfovre (pegcetacoplan) or Izervay (avacincaptad pegol) for the treatment of other conditions, including but not limited to geographic atrophy (GA) secondary to Stargardt disease, GA secondary to cone rod dystrophy, GA secondary to toxic maculopathies, or GA secondary to any disease other than age-related macular degeneration. Subjects with geographic atrophy secondary to any other condition, other than age-related macular degeneration, were excluded from the approval trials for Syfovre (pegcetacoplan) and Izervay (avacincaptad pegol). Therefore, it is unknown whether Syfovre (pegcetacoplan) and Izervay (avacincaptad pegol) are effective and safe in treating geographic atrophy resulting from conditions other than AMD.

Safety[12 13]

- In pivotal trials for Syfovre (pegcetacoplan) and Izervay (avacincaptad pegol), adverse events occurred at high rates in both the active treatment and sham-treated groups. In the trials, new onset wet AMD (or CNV) occurred at a higher rate in the active treatment groups compared to the sham-treated groups, at a rate of 12% for both Syfovre (pegcetacoplan) and Izervay (avacincaptad pegol) at 24 and 18 months, respectively. Other common adverse events noted in pivotal trials were increased intraocular pressure, conjunctival hemorrhage, blurred vison, vitreous floaters, and eye pain.

Dosing [12 13]

Medication	Dose	Frequency	Maximum Treatment Duration
Syfovre (pegcetacoplan)	15 mg (0.1ml of 150mg/ml solution) into each affected eye	Monthly (every 25 days) **OR** every Other Month (every 60 days)	NONE
Izervay (avacincaptad pegol)	2 mg (0.1 ml of 20mg/ml solution) into each affected eye	Monthly (every 28 days)	1 year maximum per prescribing information

Appendix 1: Terminology

Terminology	**Synonyms/Definitions**
Geographic atrophy	Advanced (late) stage dry AMD (atrophic lesions in the retina cause progressive degeneration of photoreceptors, retinal pigment epithelium, and choriocapillaris).
Dry age-related macular degeneration (dry AMD)	Non-exudative AMD, non-neovascular AMD, atrophic AMD
Foveal	Sub-foveal
Non-Foveal*****	Extrafoveal, perifoveal, outside of the fovea
Bilateral	In both eyes
Unilateral	In a single eye
Multifocal	Multiple lesions
Unifocal	Single lesion
Choriocapillaris	Capillaries that nourish the outer layers of the retina
Wet age-related macular degeneration (wet AMD)	Exudative AMD, neovascular AMD, choroidal neovascularization (CNV)

*** Izervay is covered ONLY for non-foveal geographic atrophy secondary to AMD**

Cross References
Complement inhibitors, Medication Policy Manual, Policy No. dru385

Codes	Number	Description
HCPCS	J2782	Injection, avacincaptad pegol (Izervay) 0.1mg
HCPCS	J2781	Injection, pegcetacoplan (Syfovre) 1mg

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Revision History

Revision Date	Revision Summary
6/20/2024	• Limits use to diagnosis of geographic atrophy (GA), secondary to age-related macular degeneration (AMD). • Izervay (avacincaptad pegol) requires an additional criterion that the GA secondary to AMD is located outside of the foveal center.

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Medication Policy Manual

Policy No: dru766

Topic: Gene therapies for sickle cell disease

- Casgevy (exagamglogene autotemcel)
- Lyfgenia (lovotibeglogene autotemcel)

Date of Origin: January 15, 2024

Committee Approval Date: June 20, 2024

Next Review Date: 2025

Effective Date: July 15, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Medications in this policy are gene therapies approved by the FDA to treat sickle cell disease (SCD).

PLEASE NOTE:

This policy does not apply to Casgevy (exagamglogene autotemcel) for use in beta thalassemia. Please refer to policy dru698 gene therapies for beta thalassemia for coverage details.

Policy/Criteria

Most contracts require pre-authorization of gene therapies for sickle cell disease (SCD) prior to coverage.

I. Gene therapies for SCD are considered investigational, except for those situations specifically addressed in the policy criteria below.

PLEASE NOTE: Under this criterion, any products not specifically addressed in this policy will be considered investigational.

II. Continuation of therapy (COT): Gene therapies for SCD may be considered medically necessary for COT when full policy criteria below are met, including quantity limit. However, Gene therapies for SCD are not coverable for repeated doses and are not coverable if a patient has previously received prior gene therapy for SCD.

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

III. New starts (treatment naïve patients): Gene therapies for SCD may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A and B below are met.

A. A diagnosis of **sickle cell disease** (SCD), established by a hematologist, when there is clinical documentation that all criteria (1 through 5) below are met:

1. The SCD is genetically confirmed as having the **HbSS genotype**.

AND

2. The patient is 12 years of age or older at the time of infusion.

AND

3. Standard therapy with hydroxyurea is ineffective after at least 6 months of therapy, unless not tolerated, or use is contraindicated. If unable to tolerate hydroxyurea, dose lowering attempts must be made to achieve the maximally tolerated therapeutic doses.

AND

4. Documentation of at least two vaso-occlusive crises (VOCs) in the prior 12-month period (as defined in *Appendix 1*).

AND

5. No prior hematopoietic stem cell transplantation (HSCT).

AND

B. The patient is a suitable candidate for gene therapies for SCD and meets all of the following criteria (1, 2, and 3) below:

1. No prior use of gene therapy (see *Appendix 2*).

AND

2. Patient is fit for therapy, as defined by meeting all the criteria (a, b, and c) below.

a. The patient has a Karnofsky or Lansky performance status (KPS) of at least 80 (or ECOG performance status of 0 or 1; the patient is ambulatory and able to carry out work of a light or sedentary nature).

AND

b. The patient has adequate and stable kidney, liver, and cardiac function (provider attestation).

AND

c. The patient has no active systemic infections (including, but not limited to HCV, HBV, and HIV infection) (provider attestation).

AND

3. Treatment with HSCT is contraindicated (including, but not limited to lack of a Human leukocyte antigen (HLA) matched related donor, comorbidities, and age).

PLEASE NOTE: Suitability for gene therapy must be documented in recent clinical documentation (such as in chart notes, laboratory reports), which MUST include evaluation for HSCT [bone marrow transplant (BMT)].

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Gene Therapies for SCD coverable only under the medical benefit (as provider-administered medications).

B. When pre-authorization is approved, Gene Therapies for SCD will be authorized in quantities of one treatment course per lifetime.

C. Additional infusions of Gene Therapies for SCD will not be authorized.

IV. Investigational Uses

A. Repeated doses of Gene Therapies for SCD or any other gene therapy products for SCD, including for gene therapy previously given as part of a clinical trial.

B. Unless otherwise specified in the coverage criteria above, Gene therapies for SCD are considered investigational when used for all other conditions, including, but not limited to:

1. ***Lyfgenia (lovotibeglogene autotemcel) only:*** Beta-thalassemia.

2. SCD genotypes other than HbSS.

3. Use in combination with another gene therapy for SCD.

Position Statement

Summary

- Gene therapies for sickle cell disease (SCD) are ex-vivo therapies that have received FDA approval and include the following:
    * Casgevy (exagamglogene autotemcel), a novel clustered regularly interspaced short palindromic repeats **(**CRISPR) and Cas9 gene-editing cell therapy, that targets BCL11A gene to increase production of fetal Hb.
    * Lyfgenia (lovotibeglogene autotemcel) uses a lentiviral vector to encode a functional copy of the beta globin gene, to produce anti-sickling hemoglobin (Hb).
- Gene therapies for SCD are a one-time IV infusion. However, they are very complex, high-cost therapy and require several phases of administration, extended hospitalization, and extensive supportive care, similar to a hematopoietic stem cell transplant (HSCT).
- The intent of this policy is to allow for coverage of gene therapies for SCD in patients with refractory SCD, a confirmed HbSS genotype, multiple vaso-occlusive crises (VOCs) per year despite standard SCD therapy, and who are clinically suitable to receive gene therapies for SCD.
- Current available evidence for gene therapies for SCD is limited to small, single-arm, non-randomized trials that evaluated freedom from severe VOCs.
    * At the most recent data analyses of the pivotal trials for Casgevy and Lyfgenia, a majority of patients were severe VOC-free for a year or more.
    * However, the long-term impact of these gene therapies for SCD on other clinically relevant outcomes, such as overall survival (OS), is currently unknown.
- SCD standard of care therapies, including hydroxyurea and HSCT, have proven long-term efficacy. However, they are not effective for all patients with SCD (recurrent VOCs despite treatment) or are not tolerated (hydroxyurea). In addition, many patients with SCD do not have an available HLA-matched related donor for HSCT or are not suitable candidates for HSCT. For these specific populations, the potential benefit of these gene therapies for SCD may outweigh the risks.
- Currently, there is insufficient evidence to establish the safety and efficacy in other settings, including other genotypes for SCD. Additional trials are ongoing.
- Gene therapies for SCD may be covered for up to one dose per lifetime. There is no data on the safety or efficacy of repeated doses, or use of more than one gene therapy for SCD.

Disease Background[1-3]

- Sickle cell disease (SCD), is a rare, recessive hemolytic anemia, caused by a mutation in the beta-globin gene. It is characterized by the formation of sickle hemoglobin (HbS), which is rigid and less flexible than fetal hemoglobin (HbF) or normal adult hemoglobin (Hb).
- Patients with SCD experience acute and chronic debilitating pain episodes as well as other events related to vaso-occlusion, referred to as vaso-occlusive crises/events (VOCs/VOEs). VOCs can lead to significant morbidity and mortality, with need for

acute care (unscheduled office visits, emergency department visits, and/or hospitalizations) and a negative impact on quality of life.

- Symptoms of SCD include episodes of severe pain, fatigue, anemia, acute chest syndrome (ACS), and infections, with chronic complications consisting of pulmonary hypertension, renal impairment, hepatotoxicity, splenic dysfunction, and stroke.

Clinical Efficacy

Casgevy (exagamglogene autotemcel)[1 4-6]

- The safety and efficacy of Casgevy (exagamglogene autotemcel) was established primarily on results from the ongoing CLIMB SCD-121 study (n=44), a small phase 2/3, non-randomized, open-label, single arm trial in patients with genetically confirmed SCD.
  - * Patients were aged 12 to 35
  - * All patients had severe SCD defined as at least two severe VOCs per year each of the previous two years, with the mean of VOC incidence for enrolled patients of 4.1 over the previous two years. Severe VOCs were defined as either an acute pain event requiring a medical office visit which included receiving pain medications or red blood cell transfusion (RBCTs), an ACS event, priapism ≥ 2 hours, or splenic sequestration.
  - * All patients were fit for Casgevy (exagamglogene autotemcel) therapy, defined as having a Karnofsky or Lansky performance status ≥ 80, adequate organ function, no active infections, clinically stable, and eligible for a HSCT but without an HLA-matched related donor. Patients with severe liver, renal, or cardiac dysfunction and those with a prior HSCT were excluded from trial enrollment.
  - * The trial enrolled of both HbSS and HbSβ^0 genotypes, However, 40 patients (91%) had an HbSS genotype while only three (7%) were HbSβ^0.
  - * The primary endpoint was the number of patients free from severe VOCs for 12 consecutive months.
  - * At the most recent available data cut-off (June 2023), 29 of the 31 eligible patients for the primary endpoint were severe VOC-free for 12 consecutive months (93.5%, P<0.0001), with the mean duration of effect of 22.3 months.
  - * The number of HbSβ^0 patients included in the most recent data cut is unknown. Given the limited number of patients with HbSβ^0 enrolled in the trial (n=3), the efficacy and safety of Casgevy (exagamglogene autotemcel) in patients with a genotype other than the HbSS genotype is unknown at this time.
  - * In the near future, additional follow up data is expected, further evaluating the durability and safety of Casgevy (exagamglogene autotemcel) in other SCD genotypes.
  - * Patients undergo myeloablative chemotherapy prior to Casgevy (exagamglogene autotemcel) infusion, with patients in the CLIMB 121-SCD trial requiring a median of 27 days of inpatient hospitalization from conditioning to discharge.

- At this time, the safety and efficacy of Casgevy (exagamglogene autotemcel) in SCD genotypes other than HbSS is uncertain. Therefore, the use of Casgevy (exagamglogene autotemcel) in any SCD genotype other than HbSS is considered investigational.

Lyfgenia (lovotibeglogene autotemcel)[1 7-9]

- The safety and efficacy of Lyfgenia (lovotibeglogene autotemcel) was established primarily from cohort C results in the ongoing HGB-206 study (n=36), a small phase 1/2 nonrandomized, open-label, single arm trial in patients with genetically confirmed SCD.
    * Patients in cohort C were aged 12 to 50. All patients had severe SCD defined as ≥ 4 severe vaso-occlusive crises (VOCs) in the previous two years, despite prior hydroxyurea use that had been treated for SCD for at least 24-months.
    * All patients were fit for Lyfgenia (lovotibeglogene autotemcel) therapy, defined as having adequate organ function, no active infections, and clinically stable. Patients with severe liver, renal, or cardiac dysfunction and those with a prior HSCT were excluded from trial enrollment.
    * The trial protocol allowed for enrollment of HbSS, HbSβ$^+$ and HbSβ^0 genotypes. However, all patients enrolled had an HbSS genotype.
    * The primary endpoint was the number of patients with complete resolution of severe vaso-occlusive events (VOEs) starting six months after the infusion until 18 months post infusion (one year free of severe VOEs).
    * Severe VOEs were defined as an event with no other cause than vaso-occlusion that required one of the following:
        - Hospital or ER visit that exceed 24 hours.
        - At least two visits to a day unit or ER during a 72-hour period (with both requiring IV treatment.
        - Priapism lasting more than two hours and leading to medical facility visit.
    * At the most recent available data cut-off (August 2022), 28 of the 32 patients eligible for the primary endpoint had complete resolution of severe VOEs for 12 consecutive months (88%), with the median follow up of duration of 32 months.
    * Given that HbSS genotypes were the only genotypes enrolled in the pivotal trial, the efficacy and safety of Lyfgenia (lovotibeglogene autotemcel) in patients with a genotype other than the HbSS genotype is unknown at this time.
    * In the near future, additional follow up data is expected, further evaluating the durability and safety of Lyfgenia (lovotibeglogene autotemcel) in other SCD genotypes.
    * Patients undergo myeloablative chemotherapy prior to Lyfgenia (lovotibeglogene autotemcel) infusion, with patients in the HGB-206 trial requiring a median of 36 days of inpatient hospitalization from conditioning to discharge.
- At this time, the safety and efficacy of Lyfgenia (lovotibeglogene autotemcel) in SCD genotypes other than HbSS is unknown. Therefore, the use of Lyfgenia (lovotibeglogene autotemcel) in any SCD genotype other than HbSS is considered investigational.

Clinical Guidelines/Standard of Care Treatment[1-3]

- The treatment of patients with SCD requires a multidisciplinary approach due to the number of complications associated with the disease.
- Current treatment approaches for patients with SCD mainly address reducing vaso-occlusive crises (VOCs), both frequency and severity.
- Guidelines recommend hydroxyurea as first-line treatment, for at least six months at the maximum tolerated dose. Clinical response to hydroxyurea may take up to six months.
- Other available treatment options for SCD include Oxbryta (voxelotor), Adakveo (crizanlizumab), and Endari (L-glutamine). However, none of these medications are included in guidelines. All have shown less efficacy when indirectly compared to hydroxyurea.
- The key components of symptomatic relief consist of red blood cell transfusion (RBCTs) and analgesics.
- Currently, HSCT is the only proven cure for SCD (>90% success rate), with the greatest benefit seen in young patients. Guidelines recommend HLA-matched related HSCT in patients with recurrent VOCs despite optimal standard of care.
- However, use of HSCT is limited by availability of HLA-matched related donors. Only 15-20% of eligible patients will have a matched related donor. and the clinical stability of the patient being treated (adequate organ function, comorbidities, age etc.).

Safety[1 4 8]

- The most common grade ≥ 3 treatment-emergent adverse events (AEs) seen during pivotal trials with gene therapies for SCD were thrombocytopenia, neutropenia, anemia, leukopenia, febrile neutropenia.
- The AEs noted above are consistent with those typically seen with the myeloablative conditioning regimen used prior to the gene therapy for SCD infusion.
- Long-term safety data is very limited as these trials are still ongoing, with a small sample size and a short treatment duration for a chronic disease.
- Additional safety data is needed to establish potential long-term toxicities that may be associated with these novel gene therapies for SCD, including the risk for malignancies or off target mutations.

Appendix 1:

Definition of vaso-occlusive crises (VOCs)[1]
Any event having no other cause than vaso-occlusion resulting in one of the following: - Acute pain episode/crises severe enough to require a visit to a medical facility for which the patient received either pain medication and/or a red blood cell transfusion (RBCT). - Acute chest syndrome. - Priapism ≥ 2 hours - Splenic or hepatic sequestration

Appendix 2:

Gene Therapies [a]
- Casgevy (exagamglogene autotemcel) - Lyfgenia (lovotibeglogene autotemcel) - Zynteglo (betibeglogene autotemcel) - Chimeric antigen receptor (CAR) T-cell therapies - Roctavian (valoctocogene roxaparvovec) - Hemgenix (etranacogene dezaparvovec)

[a] Including, but not limited to these gene therapies

Cross References
Medications for Sickle Cell Disease, Medication Policy Manual, Policy No. dru628
Gene therapies for beta thalassemia, Medication Policy Manual, Policy No. dru698

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Revision History

Revision Date	Revision Summary
6/20/2024	Clarified HLA-matched related donor in criteria.
3/21/2024	Updated cross-references.
12/07/2023	New policy (effective 1/15/20204). Policy intent is to allow coverage of gene therapies for sickle cell disease (SCD) in patients with SCD, confirmed HbSS genotype, that have failed standard SCD therapy, having multiple vaso-occlusive crises (VOCs) per year, and are clinically suitable to receive gene therapies for SCD.

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Medication Policy Manual **Policy No:** dru773

Topic: Medications for molluscum contagiosum **Date of Origin:** April 15, 2024

- Ycanth, cantharidin topical solution
- Zelsuvmi, berdazimer topical gel

Committee Approval Date: September 19, 2024 **Next Review Date:** 2025

Effective Date: December 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Medications included in this policy are used for the treatment of molluscum contagiosum (MC), a common viral infection of the skin resulting in the formation of raised lesions.

Policy/Criteria

Most contracts require pre-authorization approval of medications for molluscum contagiosum prior to coverage.

I. Continuation of therapy (COT): Medications for molluscum contagiosum (as listed in *Table 1*) may be considered medically necessary for COT when full policy criteria below are met, including diagnostic criteria (at baseline), and quantity limit.

Please note: *Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Medications for molluscum contagiosum (as listed in *Table 1*) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that following criterion A and B below are met.

A. A **diagnosis of molluscum contagiosum (MC)** has been established and criteria 1 or 2 below are met:

1. MC lesions have been present for at least 6 months.

OR

2. The MC lesions are extremely bothersome due to itching, pain, location, concern for spread, concomitant atopic dermatitis, or a bacterial infection. (provider attestation)

AND

B. The **existing** MC infection has not previously been treated with a medication for MC listed in this policy (see *Table 1*).

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Ycanth (cantharidin solution) coverable only under the medical benefit (as a provider-administered medication).

B. Pharmacy Services considers Zelsuvmi (berdazimer gel) coverable only under the pharmacy benefit (as self-administered medication).

C. When pre-authorization is approved, medications for molluscum contagiosum will be authorized in the following quantities as outlined in *Table 1* below.

Table 1: Medications for molluscum contagiosum

Product	Quantity Limit
Ycanth (cantharidin solution)	Up to 8 applicators (one treatment course) per year (max 2 applicators every 21 days for 12 weeks).
Zelsuvmi (berdazimer gel)	Up to 3 cartons (one treatment course) per year (1 carton every 4 weeks for 12 weeks).

IV. Medications for molluscum contagiosum (MC) are considered investigational when used for all other conditions, including but not limited to:

A. Treatment of MC lesions beyond 12 weeks.

B. Sequential use for the same infection, or combination use with each other (see *Table 1* for included products).

Position Statement

Summary

- Medications for molluscum contagiosum (MC) are topically administered medications approved for the treatment of MC and include the following:
  * Ycanth (cantharidin), a blistering agent (vesicant), available as a solution that must be applied by a trained healthcare provider.
  * Zelsuvmi (berdazimer), a nitric oxide releasing agent, available as a gel that can be applied at home.
- The intent of the policy is to allow coverage of medications for MC in patients with a confirmed diagnosis of MC, when lesions are persistent or extremely bothersome, and have not been previously treated with a medication for MC, as detailed in the above coverage criteria.
- Medications for MC received full approval by the FDA based on significant improvement in the percent of patients achieving complete clearance of MC lesions after 12 weeks compared to vehicle, a relevant endpoint in MC that is considered clinically curative. However, due to the self-resolving nature of MC and the small sample size of the trials, the true clinical impact of medication for MC is uncertain.
- MC is a self-limiting disease and typically resolves in six to twelve months. In healthy patients, treatment is frequently not needed. Therefore, treatment of non-bothersome lesions prior to 6 months is not covered.
- The effectiveness of one medication for MC (as listed in *Table 1*) relative to another is unknown, given the lack of comparative clinical trials.
- Medications for MC may be covered at the doses proven to be safe and effective in the clinical trials (as outlined in *Table 1* of the coverage criteria above). The safety and effectiveness of higher doses, use beyond 12 weeks, and repeat dosing for the same infection has not been established.
- Use of medications for MC in clinical settings other than described in the coverage criteria is considered investigational.

Disease Background [1-3]

- MC is a common, highly contagious, viral infection of the skin, primarily affecting children. It is characterized by small, smooth, and firm lesions on the skin.
- Transmission of MC is common and occurs through direct patient-to-patient contact and can be spread to other parts of one's own body. MC remains contagious until the lesions resolve, which is when the disease is considered cured.
- In most healthy patients, MC is self-resolving without scaring in 6-12 months; however, it can persist for much longer.

- MC lesions are typically benign. However, patients can still suffer discomfort due to itching, pain, secondary bacterial infections, worsening of atopic dermatitis (AD) or potential scarring.
- Currently, no consensus guidelines exist for treatment of MC due to the self-limiting nature of the infection. However, the American Academy of Dermatology (AAD) and the Centers for Disease Control and Prevention (CDC) state treatment of MC may be recommended in patients that have extremely bothersome lesions due to itching, pain, genital location, history of underlying atopic disease, concurrent bacterial infection, or a concern for spread.

Clinical Efficacy

Ycanth (cantharidin) solution for MC[1 4 5]

- The efficacy of Ycanth (cantharidin) was established by two identical phase 3, multicenter, randomized, double-blind, vehicle-controlled trials (CAMP-1 and CAMP-2), which included a total of 528 adult and pediatric patients with MC.
    * All patients were ≥ 2 years of age and had a diagnosis of MC with treatable lesions (lesions close to mucosal membranes or eyelids were excluded).
    * Patients had an average age of 7 years, lesion count of 21, and had been diagnosed with MC for over 4 months.
    * Patients were randomized 3:2 to receive Ycanth (cantharidin) or a vehicle control to be applied every 3 weeks in office for a maximum 4 applications (days 0, 21, 42 and 63).
    * The primary endpoint in both trials was the percent of patients achieving complete clearance of all treatable MC lesions (present at baseline or appearing during trial) compared to the vehicle control at day 84, a clinically meaningful endpoint in MC as complete clearance of lesions is considered clinically curative.
- Ycanth (cantharidin) demonstrated significant rates of improvement in the percentage of patients achieving a complete clearance of treatable MC lesions compared to the vehicle control at 84 days in both CAMP-1 and CAMP-2 trials (29% and 40% improvement over vehicle respectively.)
- However, short trial duration, lack of an active comparator, and the self-resolving nature of MC limit the certainty of effect with Ycanth (cantharidin) treatment.
- Efficacy and safety of Ycanth (cantharidin) use past 12 weeks is unknown and is considered investigational.

Zelsuvmi (berdazimer) gel for MC[6-8]

- The efficacy of Zelsuvmi (berdazimer) was established from the results of two phase 3, multicenter, randomized, double-blind, vehicle-controlled trials: the pivotal B-SIMPLE4 trial and the supportive B-SIMPLE2 trial. These trials included a total of 1,246 adult and pediatric patients with MC, with the majority of those included in the larger more robust B-SIMPLE4 trial (n=891).
    * All patients were at least 6 months of age and had a diagnosis of MC with 3-70 lesions (lesions close to mucosal membranes or eyelids were excluded).
    * Patients had an average age of 6.6 years, lesion count of 20, and had been diagnosed with MC for of over 6 months.

    * Patients were randomized 1:1 in B-SIMPLE4 or 2:1 in B-SIMPLE2 to receive Zelsuvmi (berdazimer) or a vehicle control to be applied once daily for a total of 12 weeks.
    * The primary endpoint in both trials was the percent of patients achieving complete clearance of all MC lesions (present at baseline or appearing during trial) compared to the vehicle control at week 12, a clinically meaningful endpoint in MC as complete clearance of lesions is considered clinically curative.
- Zelsuvmi (berdazimer) demonstrated significant rates of improvement in the percentage of patients achieving a complete clearance of MC lesions compared to the vehicle control at 12 weeks in the pivotal B-SIMPLE4 trial (13% improvement over vehicle).
- Although Zelsuvmi (berdazimer) showed an improvement over vehicle in the complete clearance of MC lesions in the supportive B-SIMPLE2 trial, it failed to meet statistical significance (9% improvement over vehicle, p=0.062)
- Short trial duration, lack of an active comparator, inconsistent efficacy results across trials, and the self-resolving nature of MC limit the certainty of effect with Zelsuvmi (berdazimer) treatment.
- Efficacy and safety of Zelsuvmi (berdazimer) use past 12 weeks is unknown and is considered investigational.

Investigational Uses[4 6 7]

- Medications for MC (see *Table 1*) use past 12 weeks, combination use, or sequential use of each product for the same infection has not been studied; therefore, use in these instances is considered investigational.

Safety[5]

- Ycanth (cantharidin) solution has warnings for toxicities associated with improper administration and flammability, even after drying. Therefore, it must be administered by a trained healthcare professional.

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Revision History

Revision Date	Revision Summary
9/19/2024	No criteria changes with this annual review.
3/21/2024	New policy for medications for molluscum contagiosum: • Added newly FDA-approved Ycanth (cantharidin) solution and Zelsuvmi (berdazimer) gel, with intent to allow coverage of medications for MC in patients with a confirmed diagnosis of MC, in which lesions have been present for at least 6 months, or for lesions that are extremely bothersome, and have not been previously treated with a medication for MC as detailed in the above coverage criteria.

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Medication Policy Manual | **Policy No:** dru774

Topic: Loqtorzi, toripalimab-tpzi | **Date of Origin:** April 15, 2024

Committee Approval Date: September 19, 2024 | **Next Review Date:** 2025

Effective Date: January 1, 2025

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Loqtorzi (toripalimab) is an intravenously administered immunotherapy used in the management of nasopharyngeal carcinoma (NPC). It belongs to a class of medications called programmed death receptor-1 (PD-1) blocking antibodies.

Policy/Criteria

Most contracts require pre-authorization approval of Loqtorzi (toripalimab) prior to coverage.

I. Continuation of therapy (COT): Loqtorzi (toripalimab) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Loqtorzi (toripalimab) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A, B, and C below are met:

A. A diagnosis of **nasopharyngeal carcinoma (NPC)**, recurrent locally advanced (unresectable) or metastatic.

AND

B. Loqtorzi (toripalimab) will be used in one of the following settings (1. or 2.):

1. In the first-line setting when both criteria (a and b) are met:

a. Used in combination with cisplatin and gemcitabine.

AND

b. No prior systemic therapy for recurrent or metastatic disease.

OR

2. In the subsequent-line setting when both criteria (a and b) are met:

a. Loqtorzi (toripalimab) is used as monotherapy.

AND

b. There has been disease progression on or after a platinum-containing chemotherapy regimen.

AND

C. No prior programmed death receptor-1 (PD-1) blocking antibody (PD-1 inhibitor) or programmed death-ligand 1 (PD-L1) blocking antibody (PD-L1 inhibitor) therapy. (see *Appendix 1*)

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy services considers Loqtorzi (toripalimab) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Loqtorzi (toripalimab) will be authorized in the following quantities:

- ***In combination with chemotherapy:*** For 24 weeks in doses up to 240 mg every three weeks until disease progression, or for up to 24 months.
- ***As monotherapy:*** For 24 weeks in doses up to 3 mg/kg every two weeks until disease progression.

C. Reauthorization: Authorization **shall** be reviewed at least every 24 weeks for documented benefit. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met. Specifically, documentation that the medication is providing clinical benefit, including disease stability or improvement, and lack of disease progression, based on an assessment of change in tumor burden. If there is documentation of potential disease progression, a shortened authorization (up to three months) may be approved to allow time for clarification of response to Loqtorzi (toripalimab), including clinical re-evaluation of the patient and reimaging.

PLEASE NOTE: Additional doses of Loqtorzi (toripalimab) will not be authorized without a documented recent assessment by the treating provider (such as oncologist) with objective evidence of response to therapy, such as by re-imaging and use of iRECIST criteria.

IV. Loqtorzi (toripalimab) is considered investigational when used for all other conditions.

Position Statement

Summary

- Loqtorzi (toripalimab) is an intravenously administered programmed death receptor-1 (PD-1) blocking antibody. It is indicated for the treatment of adult patients with metastatic or locally advanced (unresectable) nasopharyngeal carcinoma (NPC).
- The intent of this policy is to cover Loqtorzi (toripalimab) in settings where it has been studied and shown to be safe and effective, as detailed in the coverage criteria, with consideration for other available treatment options.
    * Where there is lack of proven additional benefit and/or lack of demonstrated health outcome (such as overall survival or improved quality of life) relative to alternative therapies, use of Loqtorzi (toripalimab) alone or in combination with other therapies is not coverable ("not medically necessary" or "investigational").
    * It is important to note that the fact that a medication is FDA approved for a specific indication does not, in itself, make the treatment medically reasonable and necessary.
- Many of the clinical indications for immunotherapies (PD-1, PD-L1, and others) have been approved by the FDA and endorsed by clinical guidelines based on surrogate measures such as overall tumor response rate (ORR) and progression-free survival (PFS) which are not proven to accurately predict clinically important outcomes such as improved overall survival or improved quality of life.
- The initial approval for Loqtorzi (toripalimab) was based on trial data in locally advanced or metastatic NPC. NPC is classified as a head and neck cancer; however, it is generally more difficult to treat so patients with NPC have historically been excluded from head and neck cancer clinical trials. Loqtorzi (toripalimab) is currently the only PD-1 inhibitor therapy that has been specifically studied in patients with NPC.
- The National Comprehensive Cancer Network (NCCN) guidelines include Loqtorzi (toripalimab) among the recommendations for front- (in combination with chemotherapy) or subsequent-line (as a monotherapy) treatment of advanced NPC that is not amenable to curable surgery or curable radiotherapy.
- As with other PD-1/PD-L1 inhibitor therapies the primary adverse effects of concern with Loqtorzi (toripalimab) are immune-mediated toxicities (e.g., endocrinopathies, colitis, hepatitis).
- Loqtorzi (toripalimab) was studied and FDA approved in the doses listed in the product prescribing information. Use of doses or frequencies exceeding these quantities are considered investigational.
- Optimal sequencing of chemotherapy and immunotherapy in many cancers is unknown or the data is evolving. Currently, sequential use of immunotherapies is not supported by current evidence. Specifically, there is no evidence to support the sequential use of different PD-1 or PD-L1 inhibitors once there is disease progression on prior PD-1 or PD-L1 inhibitor therapy, as well as use of adjuvant PD-1/PD-L1 inhibitor after neoadjuvant PD-1/PD-L1 inhibitor therapy (unless explicitly listed in the coverage criteria). Therefore, the use of sequential courses of PD-1/PD-L1 immunotherapy is not coverable.

- There are ongoing studies using Loqtorzi (toripalimab) in a variety of other cancers. However, although initial evidence may be promising, the potential for clinical benefit in these conditions is still being investigated. Therefore, use in settings other than that which is described above are considered investigational.
- *Reauthorization Criteria*: When coverage criteria are met, Loqtorzi (toripalimab) is authorized for six months (24 weeks) of therapy, after which time documentation must be provided to establish that the medication is effective. Specifically, there must be documentation of clinical benefit, including disease stability or improvement and there is a lack of disease progression, based on an assessment of change in tumor burden.
    * The standard of care for evaluation of response to cancer immunotherapy, such as Loqtorzi (toripalimab), is use of the iRECIST criteria for assessment of tumor burden. [1]
    * The iRECIST criteria include use of quantitative and qualitative criteria for assessment of change in tumor burden for target lesions and non-target lesions. [2]
        - Quantitative measurements for target lesions (tumor size and % change)
        - Qualitative evaluation for non-target lesions (present/disappeared/ unequivocal progression)
    * Documentation of benefit must include an assessment of the most recent imaging ("restaging scans") by the treating oncologist. Given the complexity of the evaluation, including use of the iRECIST criteria, Loqtorzi (toripalimab) will not be reauthorized without an assessment of response to therapy, such a partial response (iPR), complete response (iCR), or stable disease (iSD).
    * Use of immunotherapy may result in pseudoprogression, due to immune and T-cell activation, which can appear similar to tumor flare. If there is documentation of potential disease progression ["unconfirmed progressive disease (iUPD)"], a shortened authorization (up to three months) may be approved to allow time for clarification of response to Loqtorzi (toripalimab), including clinical re-evaluation of the patient and reimaging. Guidelines recommend reimaging for iUPD after 4-8 weeks.
    * If a patient has confirmed, unequivocal new lesions (progression of disease, iPD), additional Loqtorzi (toripalimab) is not coverable. If a new lesion is equivocal, iUPD reassessment by the treating oncologist with repeat imaging would apply (as noted above).

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.

- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Background [3 4]

- Nasopharyngeal carcinoma (NPC) is classified as a head and neck cancer; however, it differs in epidemiology, histology, natural history, and response to treatment. Because it is generally more difficult to treat than head and neck cancer, patients with NPC have been historically excluded from enrollment in head and neck cancer clinical trials.
- NPC is most prevalent in Southeast Asia, especially Southern China. It is much less common in the U.S. and Western Europe.
- The two most common histological subtypes of NPC are keratinizing squamous cell carcinoma (SCC) and non-keratinizing SCC. NPC with keratinizing histology is less responsive to radiation therapy and is associated with lower survival rates. This more difficult to treat histology makes up only 2% of cases in SE Asia, but up to 25% of cases in North America.
- NPC tends to metastasize early. At the time of diagnosis lymph node metastasis is present in 75% to 90% of cases, and distant metastasis is present in 5% to 11% of cases.

Clinical Efficacy

- The efficacy of Loqtorzi (toripalimab) in locally advanced (unresectable) or metastatic nasopharyngeal carcinoma (NPC) was evaluated in two pivotal studies:

  Front-line setting in combination with chemotherapy [JUPITER-02] [5]

  * This randomized, double-blind controlled trial enrolled patients with primary recurrent or metastatic NPC whose disease was not amenable to local/regional or curative treatment and who had no prior systemic therapy in this setting.
  * The study was conducted in Southeast Asia. Nearly all (99%) patients in the study had NPC with nonkeratinizing histology.
  * Seventy-five percent of patients had NPC tumors that were PD-L1 positive (≥1%).
  * Patients received either Loqtorzi (toripalimab) in combination with standard-of-care platinum-based chemotherapy or chemotherapy alone (placebo group).
  * Median progression-free survival (PFS) was 11.7 months and 8 months in the Loqtorzi (toripalimab) and placebo groups, respectively. The data for the overall survival endpoint is not mature.
  * Study limitations include lack of representation of tumors with keratinizing histology which is present in up to 25% of cases in the U.S., the high proportion (75%) of PD-L1-postive tumors which may have driven the PFS results, and the

use of a surrogate endpoint that has not been shown to predict improvement in clinical outcomes.

Subsequent-line setting as monotherapy [POLARIS-02] [6]

* This uncontrolled (single-arm) observational study enrolled patients with recurrent or metastatic (98%) NPC that progressed on or after standard-of-care platinum-based chemotherapy.
* The study was conducted in China. Nearly all (96%) patients had NPC with nonkeratinizing histology, the predominant histology in this geographic region.
* All patients received Loqtorzi (toripalimab) as monotherapy every two weeks until disease progression.
* The study evaluated tumor response as the primary endpoint. The objective response rate (ORR) was 20.5% with a complete response rate of 2.6%.
* Study limitations include high potential for bias due to single-arm study design, lack of representation of tumors with keratinizing histology which is present in up to 25% of cases in the U.S. and generally has poorer outcomes, and use of a surrogate endpoint which is not predictive of clinical benefit.

- NPC is considered a head and neck cancer; however, because it is more difficult to treat, patients with NPC have historically been excluded from head and neck cancer clinical trials. Loqtorzi (toripalimab) is the first PD-1 inhibitor to specifically be studied in NPC. Though it shows promise in this treatment setting, there is no data to date showing that it improves clinical outcomes such as overall survival or quality of life.

Guidelines [4]

- The National Comprehensive Cancer Network (NCCN) Head and Neck Cancer guideline lists Loqtorzi (toripalimab) among potential first- and subsequent-line therapy options for recurrent or metastatic NPC when surgery and radiation are not curative options.

Investigational Uses [7]

- Loqtorzi (toripalimab) is currently being studied in several other types of cancer including other head and neck cancers, such as squamous cell carcinoma of the head and neck (SCCHN), and small cell lung cancer (SCLC). However, to date, Loqtorzi (toripalimab) has not been shown to be an effective therapy for any other type of cancer.

Safety [8]

- The primary adverse effects (AEs) of interest for Loqtorzi (toripalimab) include immune-mediated reactions and infusion reactions. Immune-related AEs can affect any organ system or tissue (e.g., colitis, pneumonitis, hepatitis, endocrinopathies, nephritis with renal dysfunction, and dermatologic reactions).
- Overall, the safety of Loqtorzi (toripalimab) appear to be similar to other PD-1 and PD-L1 inhibitors.

Dosing *[8]*

- Loqtorzi (toripalimab) is given via intravenous infusion over 30 to 60 minutes.
- When given in combination with chemotherapy Loqtorzi (toripalimab) is given in a dose of 240 mg every three weeks until disease progression, or for a maximum of 24 months. As a monotherapy it is dosed as 3 mg/kg every two weeks until disease progression.

Appendix 1: FDA-Approved PD-1 and PD-L1 Blocking Monoclonal Antibody Therapies [a]
Programmed death receptor-1 (PD-1) inhibitors
Jemperli (dostarlimab)
Keytruda (pembrolizumab
Libtayo (cemiplimab)
Loqtorzi (toripalimab)
Opdivo (nivolumab)
Tevimbra (tislelizumab)
Zynyz (retifanlimab)
Programmed death-ligand 1 (PD-L1) inhibitors
Bavencio (avelumab)
Imfinzi (durvalumab)
Tecentriq (atezolizumab)

[a] Or as listed on the FDA.gov website

Cross References
None

Codes	**Number**	**Description**
HCPCS	J3263	injection, toripalimab-tpzi, 1 mg

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Revision History

Revision Date	Revision Summary
9/19/2024	• **Effective 1/1/2025:** Changed reauthorization from 'may' to 'shall.' Operationally, all approvals will be for 24 weeks (6 months). Ongoing therapy (beyond 24 weeks) will be subject to reauthorization review every 24 weeks, for documentation of disease stability or improvement and lack of disease progression.
3/21/2024	New policy (effective 4/15/2024). - Limits coverage of Loqtorzi (toripalimab) to patients with locally advanced (unresectable) or metastatic nasopharyngeal carcinoma (NPC) in combination with platinum-based chemotherapy as a front-line therapy, or as a monotherapy for patients whose disease has progressed on, or after, front-line platinum-based chemotherapy. - Use is limited to patients who have not received prior PD-1/PD-L1 therapy. - All other uses are considered investigational.

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Medication Policy Manual **Policy No:** dru779

Topic: High-cost medications for cholesterol **Date of Origin:** June 1, 2024

- Evkeeza, evinacumab-dgnb
- Leqvio, inclisiran
- Nexletol, bempedoic acid
- Nexlizet, bempedoic acid/ezetimibe
- Praluent, alirocumab
- Repatha, evolocumab

Committee Approval Date: March 21, 2024 **Next Review Date:** 2025

Effective Date: June 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

High-cost medications for cholesterol work through a variety of mechanisms to treat atherosclerotic cardiovascular disease (ASCVD) and/or familial hypercholesteremia.

Policy/Criteria

Most contracts require pre-authorization approval of high-cost medications for cholesterol prior to coverage.

I. Continuation of therapy (COT): High-cost medications for cholesterol may be considered medically necessary for COT when criteria A, B, or C AND D below is met.

A. For diagnoses NOT listed in the coverage criteria below, full policy criteria must be met for coverage.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

AND

D. For Leqvio (inclisiran) only: Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, Site of Care Review, dru408].

Please note: *Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): High-cost medications for cholesterol may be considered medically necessary when criteria A and B below are met.

A. **Leqvio (inclisiran) only**: Site of care administration requirements are met [refer to Pharmacy Services Medication Policy Manual, Site of Care Review, dru408].

AND

B. At least one of the following diagnostic criterion 1, 2 or 3 below is met.

1. **Leqvio (inclisiran), Nexletol (bempedoic acid), Nexlizet (bempedoic acid/ezetimibe), Praluent (alirocumab), Repatha (evolocumab): Heterozygous familial hypercholesterolemia** (HeFH) when both criteria (a and b) are met.

a. The requested PCSK9 inhibitor has been prescribed by or in conjunction with a specialist in cardiology or lipid management

and there is clinical documentation of at least one of the following (i, ii, or iii):

i. A definitive diagnosis of FH using Simon Broome diagnostic criteria or Dutch Lipid Clinic Network criteria (see *Appendices 1 and 2*).

OR

ii. An untreated low-density lipoprotein cholesterol (LDL-C) of ≥ 190 mg/dL (or ≥ 160 mg/dL in patients less than 20 years of age) with at least one of the following:

1. Physical signs of FH, such as presence of tendon xanthomas, premature corneal arcus, tuberous xanthomas, or xanthelasma.

OR

2. Family History of FH.

OR

iii. Presence of a causal mutation for FH by DNA testing (e.g., a mutation in the LDLR, APOB, PCSK9, or LDLRAP1 genes).

b. Treatment with maximally tolerated lipid lowering therapy has failed to achieve an LDL-C of less than 100 mg/dL after at least 12 weeks of therapy. The treatment regimen must include <u>all the following</u> (i, ii, and iii), unless contraindicated or not tolerated:

i. A high-intensity statin (atorvastatin or rosuvastatin). If one high-intensity statin has not been tolerated due to statin-associated side effects, then at least one other statin must have been tried at a lower dose.

AND

ii. Ezetimibe.

AND

iii. **For Leqvio (inclisiran) only:** Praluent (alirocumab) or Repatha (evolocumab).

OR

2. **Evkeeza (evinacumab-dgnb)**, **Praluent (alirocumab), Repatha (evolocumab): homozygous familial hypercholesterolemia (HoFH)** when criteria a, b, and c below are met:

a. The requested PCSK9 inhibitor has been prescribed by or in conjunction with a specialist in cardiology or lipid management and there is clinical documentation of at least one of the following (i or ii):

i. Genetic confirmation of two mutant alleles at the *LDLR, APOB, PCSK9,* or *LDLRAP1* gene locus.

OR

ii. An untreated low-density lipoprotein cholesterol (LDL-C) of > 500 mg/dL (or a treated LDL-C of > 300 mg/dL) with either (1 or 2):

1. Cutaneous or tendon xanthoma before age 10 years.

OR

2. Evidence of heterozygous familial hypercholesterolemia in both parents.

AND

b. Treatment with maximally tolerated statin therapy has been ineffective, contraindicated, or not tolerated.

AND

c. **For Evkeeza (evinacumab-dgnb) only:** Repatha [evolocumab] or Praluent [alirocumab] therapy has been ineffective, contraindicated, or not tolerated.

OR

3. **Leqvio (inclisiran), Nexletol (bempedoic acid), Nexlizet (bempedoic acid/ezetimibe), Praluent (alirocumab), Repatha (evolocumab): clinical atherosclerotic cardiovascular disease (ASCVD) or at risk for ASCVD event** when criteria a, b, and c below are met (see *Appendix 6* for definitions of ASCVD).

a. The requested PCSK9 inhibitor has been prescribed by or in conjunction with a specialist in cardiology or lipid management.

AND

b. At least one of the following (i or ii):

i. **Primary prevention:** Pre-treatment LDL-C ≥190 mg/dL **AND** more than one high-risk condition (see Appendix 8)

OR

ii. **Secondary prevention**: The member has had at least one major ASCVD event (see Appendix 8) **AND** at least one of the following (1, 2, 3, or 4):

1. Very high risk ASCVD (see Appendix 8)

OR

2. Diabetes (DM)

OR

3. Chronic kidney disease (CKD), not on dialysis

OR

4. Pre-treatment LDL ≥190 mg/dL

AND

c. Treatment with maximally tolerated lipid lowering therapy has failed to achieve an LDL-C of less than 55 mg/dL after at least 12 weeks of therapy. The treatment regimen must include all the

following (i, ii, and iii), unless contraindicated or not tolerated.

i. A high-intensity statin (atorvastatin or rosuvastatin). If one high-intensity statin has not been tolerated due to statin-associated side effects, then at least one other statin must have been tried at a lower dose.

AND

ii. Ezetimibe.

AND

iii. **For Leqvio (inclisiran) only:** Praluent (alirocumab) or Repatha (evolocumab).

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Nexletol (bempedoic acid), Nexlizet (bempedoic acid/ezetimibe), Praluent (alirocumab) and Repatha (evolocumab) to be coverable only under the pharmacy benefit (as self-administered medications).

B. Regence Pharmacy Services considers Evkeeza (evinacumab-dgnb) and Leqvio (inclisiran) to be coverable only under the medical benefit (as provider-administered medications).

C. When pre-authorization is approved, high-cost medications for cholesterol will be authorized in the following quantities:

Medication	**Authorization Limit**
Evkeeza (evinacumab-dgnb)	Up to 15 mg/kg once monthly. For doses exceeding 1200 mg, dose rounding down to the nearest available vial size (within 10% of calculated dose) is required.
Leqvio (inclisiran)	Loading Dose: Up to 284 mg initially followed by 284 mg in 3 months. Maintenance Dose: Up to 284 mg every 6 months.
Nexletol (bempedoic acid) Nexlizet (bempedoic acid/ ezetimibe)	Up to 30 tablets per 30 days.
Praluent (alirocumab)	Up to 150 mg every 2 weeks or 300 mg every 4 weeks.
Repatha (evolocumab)	Up to 140 mg every other week or 420 mg once monthly.

D. Authorization may be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

IV. High-cost medications for cholesterol are considered not medically necessary when used for:

A. Non-familial hyperlipidemia/hypercholesterolemia.

V. High-cost medications for cholesterol are considered investigational when used for all other conditions, including but not limited to:

A. Combination use of high-cost medications for cholesterol as listed in this policy and/or Juxtapid (lomitapide).

B. Evkeeza (evinacumab-dgnb): for other causes of hypercholesterolemia, including those with heterozygous familial hypercholesterolemia (HeFH); or for prevention of cardiovascular disease.

Position Statement

Summary

- The intent of this policy is to limit coverage of high-cost medications for cholesterol to patients with a confirmed diagnosis of homozygous familial hypercholesterolemia (HoFH), heterozygous familial hypercholesterolemia (HeFH), or at high-risk for cardiovascular events, who have tried and failed lower cost therapies (as detailed in the coverage criteria).
- HeFH and HoFH may be diagnosed via clinical criteria, such as baseline LDL values, family history, and physical manifestations of FH, or through genetic testing. Commonly used diagnostic criteria include Simon Broome Diagnostic Criteria and Dutch Lipid Clinic Network Criteria for Heterozygous FH Diagnosis
    * Treatment guidelines recommend the use of a maximally tolerated high-intensity statin as first-line pharmacotherapy for patients with HeFH or HoFH, even in patients who are LDL receptor negative, as they have been shown to reduce cardiovascular (CV) and all-cause mortality.
    * National Lipid Association (NLA) treatment guidelines for HeFH recommend targeting a 50% reduction in LDL-C from baseline; however higher risk patients may require a more aggressive treatment goal of less than 100 mg/dL. Patients will generally require treatment with multiple agents to achieve LDL-C goals.
    * Non-statins may be considered in patients who are unable to reach target LDL-levels or who are statin intolerant. PCSK9 inhibitors are endorsed as add-on therapy for HeFH or HoFH.
    * In HoFH, Evkeeza (evinacumab-dgnb) has not been proven to be safer or more effective than statins or PCSK9 inhibitors but is more costly.
- Although there is no universally accepted definition of statin intolerance, most experts recommend patients have unacceptable muscle-related symptoms that resolved with discontinuation and recur with rechallenge on at least two (and preferably three)

statins.[1] Hydrophilic statins, rosuvastatin and pravastatin, tend to be associated with less muscle-side effects.

- ACC/AHA Guidelines define clinical ASCVD as acute coronary syndromes, a history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease presumed to be of atherosclerotic origin.
    * 2018 American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines on the Management of blood cholesterol recommend high-intensity statins for high-risk patients, such as those with clinical ASCVD or with HeFH. On average, high-intensity statins lower LDL-C by approximately ≥50%. Statins have been proven to reduce cardiovascular (CV) events and mortality; thus, they are the preferred treatment to reduce the risk ASCVD and recommended as the first-line treatment by multiple guidelines.
    * If additional LDL-C lowering is needed, ezetimibe is widely available as a generic and has proven safety and tolerability along with CV outcomes benefit (based on results from the IMPROVE-IT study). The addition of ezetimibe to statin therapy typically reduces LDL-C by roughly 25% in patients with hyperlipidemia.
    * Treatment with either Praluent (alirocumab) or Repatha (evolocumab) in combination with a statin modestly improved CV outcomes.
    * The use of medications with proven CV benefits is required prior to coverage of Leqvio (inclisiran) or Evkeeza (evinacumab-dgnb), as outlined in the coverage criteria, as the CV benefits of either are unknown at this time.
    * PCSK9 inhibitors appear to be well-tolerated. However, additional long-term studies and clinical experience is needed with Leqvio (inclisiran) and Evkeeza (evinacumab-dgnb).
- Evkeeza (evinacumab-dgnb) may be covered for up to 15 mg/kg every four weeks, the dose studied in clinical trials. The safety and effectiveness of higher doses have not been established. Dose rounding down to the nearest available vial size may be required within 10% of the calculated dose to reduce product waste without sacrificing efficacy. Dose rounding within 10% of a calculated dose is an accepted industry standard and has been adopted in various clinical care areas.
- High-cost medications for cholesterol have not been studied in combination with one another or Juxtapid (lomitapide).

Clinical Efficacy

Evkeeza (evinacumab)[2 3]

- The efficacy and safety of evinacumab was evaluated in ELIPSE, a phase 3, double-blind, placebo-controlled trial of patients with genetically or clinically confirmed HoFH on stable lipid-lowering therapy.
    * Patients were randomly assigned to an IV infusion of evinacumab 15 mg/kg or placebo every four weeks.
    * 63% of patients were receiving at least three lipid-modifying drugs at baseline; 94% were on a statin and 77% were on a PCSK9 inhibitor.

    * The between group decrease in LDL-C from baseline to week 24 was 49% (absolute change of -132 mg/dL), in favor of Evkeeza (evinacumab-dgnb).
    * The effects of Evkeeza (evinacumab-dgnb) on cardiovascular morbidity and mortality have not yet been determined.

Leqvio (inclisiran)

- The body of evidence supports that Leqvio (inclisiran) produces substantial reductions in LDL-C. [4 5]
    * The primary endpoint in the majority of Leqvio (inclisiran) phase 3 studies was percent change in LDL-C.
    * Reductions in LDL-C ranged from 40% to 51% in patients with clinical ASCVD or HEFH.
- Although the data continues to evolve, CV outcomes data for Leqvio (inclisiran) is not yet available.

Nexletol/Nexlizet (bempedoic acid/ezetimibe)

- The evidence of efficacy for bempedoic acid in cardiovascular disease (CVD) reduction is based on the CLEAR trial, which was a phase 3, double-blind, placebo-controlled, randomized trial in patients unwilling/unable to take guideline-recommended doses of statins. ~70% of patients had established cardiovascular disease and ~23% were on a low dose statin.[6]
- Bempedoic acid met its primary endpoint of reducing 4-point MACE (major adverse cardiovascular event; defined as death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization) by 13% and significantly reduced the risk of heart attack and coronary revascularization by 23% and 19%, respectively, compared to placebo. The median follow up was 40.6 months.[6]
- Bempedoic acid did not significantly reduce the rate of fatal or nonfatal stroke, cardiovascular death, or death from any cause compared to placebo. Reductions of LDL-C were modest.

Praluent (alirocumab)

- The ODYSSEY OUTCOMES study evaluated the impact of Praluent (alirocumab) on cardiovascular outcomes in patients with a history of acute coronary syndrome (ACS) in the past 1 to 12 months. The primary endpoint was the composite of cardiovascular death, MI, stroke, and hospitalization for unstable angina. Patients were randomized to either Praluent (alirocumab) 75 mg every two weeks or placebo. All patients were on background high-intensity statins or their maximally-tolerated dose of atorvastatin or rosuvastatin.
    * After a median follow-up of 2.8 years, Praluent (alirocumab) reduced the risk of the primary endpoint compared to placebo (9.5% vs. 11.1%, respectively; hazard ratio, 0.85; 95% CI, 0.78 to 0.93; P<0.001). The secondary endpoint of the composite of death from any cause, non-fatal MI, and non-fatal stroke also favored alirocumab compared to placebo (10.3% vs. 11.9%, respectively; hazard ratio 0.86; 95% CI 0.79 to 0.93; P<0.001).

- The body of evidence supports that Praluent (alirocumab) produces substantial reductions in LDL-C. [7 8]
    * The primary endpoint in the majority of Praluent (alirocumab) phase 3 studies was percent change in LDL-C.
    * Among ten placebo- and active controlled phase 3 studies, Praluent (alirocumab) reduced LDL-C by approximately 43 to 61 percent from baseline. The studies included a several populations, including those with HeFH and/or clinical ASCVD. Studies ranged in duration from 12 to 78 weeks. Results were statistically significant versus placebo and versus ezetimibe.
    * In patients with HoFH the mean LDL-C reduction was approximately 36%.[9]

Repatha (evolocumab)

- The FOURIER study evaluated the impact of evolocumab on cardiovascular outcomes in patients with clinical ASCVD. The primary endpoint was the composite of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization. Patients were randomized to either Repatha (evolocumab) or placebo and all patients were on background high or moderate intensity statin therapy. [10]
    * After a median follow-up of 26 months, evolocumab modestly reduced the risk of the primary endpoint compared to placebo (9.8% vs. 11.3%, respectively; hazard ratio, 0.85; 95% CI, 0.79 to 0.92; P<0.001).
    * Evolocumab also significantly reduced the risk of the key secondary composite of CV death, MI, or stroke compared to placebo (5.9% vs. 7.4%, respectively; hazard ratio, 0.80; 95% CI, 0.73 to 0.88; P<0.001). However, results for cardiovascular mortality alone were not statistically significant.
- The body of evidence supports that Repatha (evolocumab) produces substantial reductions in LDL-C. [11]
    * The primary endpoint in the majority of Repatha (evolocumab) phase 3 studies was percent change in LDL-C. Reductions in LDL-C ranged from 54% to 71% in patients with clinical ASCVD or HeFH. [11]
    * In patients with HoFH the mean LDL-C reduction was approximately 31%. [12]

Guidelines

ASCVD[1 13 14]

- The 2022 American College of Cardiology (ACC), endorsed by the National Lipid Association (NLA) Expert Consensus Decision Pathway on the Role of Non-statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk state that PCSK9 inhibitors are reasonable for patients with very high risk ASCVD who cannot achieve an ≤50% reduction in LDL-C from baseline and LDL-C <55 mg/dL while on a high-intensity statin and ezetimibe.
    * Very high risk is defined as a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk condition (see *Appendix 8*).
    * The 2018 American Heart Association (AHA)/ACC/multi-society cholesterol guideline includes patients with CKD not on dialysis as a higher-risk subset of

patients with ASCVD who may merit consideration for more intensive LDL-C lowering. Issues surrounding the use of statins and non-statin therapies in patients on maintenance dialysis are less clear. Several statin trials found no significant benefit for patients on maintenance hemodialysis in any vascular outcomes in the context of their extremely high all-cause mortality rates. No phase 3 data is available for use of high-cost medications for cholesterol in patients with dialysis, as they were excluded from trials.

* For people with diabetes and ASCVD, treatment with high-intensity statin therapy is recommended to target an LDL cholesterol reduction of ≥50% from baseline and an LDL cholesterol goal of <55 mg/dL (<1.4 mmol/L). Addition of ezetimibe or a PCSK9 inhibitor with proven benefit in this population is recommended if this goal is not achieved on maximum tolerated statin therapy.

- Thresholds of ≤50% reduction in LDL-C from baseline and LDL-C <55 mg/dL are variable and individualized based on patient characteristics and risk factors for ASCVD.
- Guidelines acknowledge that the evidence supporting the use of ezetimibe before PCSK9 inhibitors is limited. Although, patients in both PCSK9 inhibitor outcomes studies were permitted to use ezetimibe, very few did. The recommendation placing ezetimibe ahead of PCSK9 inhibitors is primarily due to wide availability as a generic and proven safety and tolerability.

HeFH

- National Lipid Association (NLA) treatment guidelines for HeFH recommend targeting a 50% reduction in LDL-C from baseline; however higher risk patients may require a more aggressive treatment goal of less than 100 mg/dL. High risk HeFH patients included those with clinically evident CHD or other atherosclerotic cardiovascular disease, diabetes, a family history of very early CHD (in men < 45 years of age and women < 55 years of age), current smoking, two or more CHD risk factors, or high lipoprotein (a) ≥ 50 mg/dL. Intensification of therapy may also be considered in patients without any of the listed previously factors, if LDL-C remains ≥ 160 mg/dL (or non-HDL cholesterol ≥ 190 mg/dL), or if an initial 50% decrease is LDL-C is not achieved. [15]
- NLA guidelines recommend statins as the initial treatment for all patients with FH. Ezetimibe, niacin, and bile acid sequestrants are considered reasonable treatment options for intensification of therapy, or for those intolerant of statins. EAS guidelines for HeFH provide generally similar treatment recommendations but recommend different target LDL levels. [15]

HOFH[16 17]

- HoFH is a very rare type of familial hypercholesterolemia (FH), an autosomal dominant lipid disease that is characterized by abnormally elevated LDL-C levels and an increased propensity for early onset cardiovascular disease.
- Genetic confirmation of two mutant alleles at the LDLR, APOB, PCSK9, or LDLRAP1 gene locus is confirmative of the presence of HoFH.

Investigational Uses

- High-cost medications for cholesterol have not been studied in combination with one another or Juxtapid (lomitapide).
- There are no published clinical trials evaluating the safety or efficacy of Evkeeza (evinacumab-dgnb) for the treatment of other causes of hypercholesterolemia, including those with heterozygous FH (HeFH) and prevention of cardiovascular disease (CVD).

Dosing considerations

- For primary hyperlipidemia, the recommended starting dose for Praluent (alirocumab) is 75 mg administered subcutaneously once every 2 weeks. For those with HoFH or HeFH on lipid apheresis or if the LDL-C response is inadequate, the dose may be increased to the maximum dose of 150 mg administered every 2 weeks. An alternative starting dose of 300 mg every 4 weeks may also be considered.[8]
- The recommended starting dose of Repatha (evolocumab) for patients with HeFH or clinical ASCVD is 140 mg once every 2 weeks or 420 mg once monthly, administered subcutaneously. The recommended starting dose for patients with HoFH is 420 mg once monthly. For patients with HoFH who are either on lipid apheresis or the LDL-C response is inadequate after 12 weeks, the dose may be increased to the maximum dose of 420 mg administered every 2 weeks.[11] However, in patients with HoFH who either require dose escalation or are undergoing LDL apheresis, Praluent (alirocumab) is often the most cost-effective option.
- The recommended dose of Leqvio (inclisiran) is 284 mg given subcutaneously as a single injection, repeated at 3 months, then every 6 months thereafter.[18]

Appendix 1: Dutch Lipid Clinic Network criteria [19]	
Criteria	**Points**
Group 1: family history	
First-degree relative with known premature (age <55 for males or < 60 for females) coronary heart disease *OR* First-degree relative with known LDL cholesterol above 95th percentile	1
First-degree relative with tendon xanthoma and/or corneal Arcus *OR* Children < 18 years with LDL cholesterol above 95th percentile	2
Group 2: clinical history	
Premature coronary heart disease (age <55 for males or < 60 for females)	2
Premature cerebral or peripheral vascular disease (age <55 for males or < 60 for females)	1
Group 3: physical examination	
(i) Tendon xanthoma	6
(ii) Corneal arcus in a person before age 45	4
Group 4: biochemical results (LDL-C)	
≥8.5 mmol/L (≥330 mg/dL)	8
6.5–8.4 mmol/L (250–329 mg/dL)	5
5.0–6.4 mmol/L (190–249 mg/dL)	3
4.0–4.9 mmol/L (155–189mg/dL)	1
Group 5: molecular genetic testing (DNA analysis)	
(i) Causative mutation shown in the LDLR, APOB, or PCSK9 genes	8
Scoring	
> 8 points: Definite FH 6-8 points: Probable FH 3-5 points: Possible FH <3 points: Unlikely FH	

Appendix 2: Simon Broome Register Diagnostic Criteria for Definitive FH [16]
Adults: Total cholesterol levels > 290 mg/dL (7.5 mmol/L) or LDL-C > 190 mg/dL (4.9 mmol/L). Children less than 16 years of age: Total cholesterol levels > 260 mg/dL (6.7 mmol/L) or LDL-C > 155 mg/dL (4.0 mmol/L). Plus at least one of the two: **1.** Physical findings: tendon xanthomas or tendon xanthomas in a first or second degree relative. **OR** **2.** DNA-based evidence of an LDL-receptor mutation, familial defective apo B-100, or a PCSK9 mutation.

Appendix 3: Risk Factors for Statin-Associated Muscle Symptoms [13 20]
Hypothyroidism
Multiple or serious co-morbidities, including reduced renal or hepatic function
Rheumatologic disorders such as polymyalgia rheumatica
Steroid myopathy
Vitamin D deficiency
Primary muscle diseases
Acute infection
Organ transplant recipients
Severe trauma
HIV
Diabetes mellitus
Major Surgery
History of creatinine kinase elevation
History of pre-existing/unexplained muscle/joint/tendon pain
Genetic factors such as polymorphisms in genes encoding cytochrome P450 isoenzymes or drug transporter
High level of physical activity
Dietary effects (excessive grapefruit or cranberry juice)
Excess alcohol
Drug abuse (cocaine, amphetamines, heroin)

Appendix 4: Examples of Drug-drug interactions that may increase the risk of skeletal muscle effects with High-Intensity Statins
Strong inhibitors of CYP 3A4 (e.g., clarithromycin, itraconazole, protease inhibitors)
Grapefruit Juice
Cyclosporine
Gemfibrozil and other fibrates
Niacin
Colchicine

Appendix 5: Contraindications to Statin Therapy [21 22]
Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels
History of rhabdomyolysis
Hypersensitivity
Nursing Mothers
Pregnancy

Appendix 6: Clinical Atherosclerotic Cardiovascular Disease (ASCVD) [13]
Acute coronary syndromes
History of coronary or other arterial revascularization
History of myocardial infarction
History of stable or unstable angina
History of stroke or transient ischemic attack (TIA)
Peripheral arterial disease presumed to be of atherosclerotic origin

Appendix 7: Statin Comparison Chart [13]		
% LDL- C Lowering	**Statin Name**	**Strength**
Low-intensity: < 30%	Fluvastatin	20 mg, 40 mg
	Lovastatin	10 mg, 20 mg
	Lovastatin ER (Altoprev)	20 mg
	Pitavastatin (Livalo)	1 mg
	Pravastatin	10 mg, 20 mg
	Simvastatin	5 mg, 10 mg
Moderate-intensity: 31% - 49%	Atorvastatin	10 mg, 20 mg
	Fluvastatin ER (Lescol XL)	80 mg
	Lovastatin	40 mg
	Lovastatin ER (Altoprev)	40 mg, 60 mg
	Pitavastatin (Livalo)	2 mg, 4 mg
	Pravastatin	40 mg, 80 mg
	Rosuvastatin	5 mg, 10 mg
	Simvastatin	20 mg, 40 mg
High-intensity: ≥ 50%	Atorvastatin	40 mg, 80 mg
	Rosuvastatin	20 mg, 40 mg

Appendix 8: AHA/ACC Definition of Very-High Risk ASCVD [13]	
Very high risk includes a history of multiple major ASCVD events or one major ASCVD event and multiple high-risk conditions.	
Major ASCVD Events	**High-Risk Conditions**
Recent ACS (in past 12 months)	Age ≥ 65 years
History of MI (other than recent ACS event)	HeFH
History of ischemic stroke	History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event
Symptomatic Peripheral arterial disease (History of claudication with ABI< 0.85, or previous revascularization or amputation)	Diabetes mellitus
	Hypertension
	Chronic Kidney Disease
	Current Smoking
	Persistently elevated LDL-C (≥ 100 mg/dL) despite maximally tolerated statin therapy and ezetimibe
	History of congestive heart failure

Cross References
Genetic Testing for Familial Hypercholesterolemia, Medical Policy Manual, Policy No. 11
Pharmacy Services Medication Policy Manual, Site of Care Review, dru408

Codes	**Number**	**Description**
HCPCS	J1305	Injection, evinacumab-dgnb (Evkeeza), 5mg
HCPCS	J1306	Injection, inclisiran (Leqvio), 1 mg

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Revision History

Revision Date	Revision Summary
3/21/2024	Effective 6/1/2024 • Combined policy including PCSK9 inhibitors, Evkeeza (evinacumab), and Nexletol/Nexlizet (bempedoic acid/ezetimibe). • ASCVD risk category expanded to include secondary prevention with diabetes, chronic kidney disease or very high LDL-C at baseline. Primary prevention covered for very high LDL-C with multiple risk factors for an ASCVD event based on guideline updates. • LDL-C goal updated to be in-line with society guidelines.

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Medication Policy Manual **Policy No:** dru780

Topic: Non-Cosmetic Use of Medications and Products

- Kybella, deoxycholic acid
- Prolaryn, glycerin/carboxymethylcellulose gel implant
- Radiesse, calcium hydroxylapatite
- Sculptra, poly-l-lactic acid

Date of Origin: April 15, 2024

Committee Approval Date: September 19, 2024 **Next Review Date:** 2025

Effective Date: January 1, 2025

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language takes precedence.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Some medications and products may be used for cosmetic and non-cosmetic purposes. The purpose of this policy is to confirm these products are not being used for cosmetic reasons. Products with potential cosmetic use may be covered when being used for a non-cosmetic purpose (e.g., HIV-associated facial lipodystrophy or vocal cord paralysis). When used for cosmetic purposes, medications and other medical products are contract excluded.

PLEASE NOTE: *This policy does not apply services that are prescribed for gender affirming care; please refer to Cross References for applicable policies*

Policy/Criteria

I. Continuation of therapy (COT): Products in *Appendix 1* may be considered medically necessary for COT when full policy criteria below are met, including quantity limit.

Please note: *Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Products in *Appendix 1* may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) confirming that the following criteria A and B below are met:

A. The requested product is not used for cosmetic purposes, defined as treatment directed at improving aesthetic appearance or changing the appearance to normal structures of the body (e.g., providing volume for wrinkles around the eyes, cheeks, lips, or neck).

AND

B. The requested product would be used for the sole purpose of treating a medical complication (e.g., HIV-associated facial lipodystrophy, vocal cord paralysis).

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers products in *Appendix 1* to be coverable under the medical benefit. Determination of coverage under the medical benefit is based on group-specific benefits, as defined in the group and member contract.

B. Continued authorization **may** be reviewed at least every 12 months.

IV. Products in *Appendix 1* are considered not medically necessary when used for cosmetic purposes, defined as treatment directed at improving aesthetic appearance or changing the appearance to normal structures (e.g., skin wrinkles, sagging cheeks, nasolabial folds, undereye hollows).

PLEASE NOTE: *This policy does not apply services that are prescribed for gender affirming care; please refer to Cross References for applicable policies.*

Position Statement

Summary

- The intent of this policy is to determine whether a medication or product is being used for a medical purpose versus a cosmetic purpose, which is defined as treatment directed at improving aesthetic appearance or changing the appearance to normal structures of the body (e.g., providing volume for wrinkles around the eyes, cheeks, lips, or neck). When performed solely to alter appearance without an associated functional impairment or medical complication, these medications and products are considered cosmetic and contractually excluded. Use for the treatment of a medical complication without a cosmetic purpose is covered and considered medically necessary.
- Coverage criteria for gender-affirming care can be found in separate coverage policies (see *Cross References* table below).

Appendix 1
Kybella (deoxycholic acid)
Prolaryn, glycerin/carboxymethylcellulose gel implant
Radiesse (calcium hydroxylapatite)
Sculptra (poly-l-lactic acid)

Cross References
Cosmetic and Reconstructive Surgery, Medical Policy Manual; Surgery, Policy No. 12
Gender Affirming Care, Medication Policy Manual, Policy No. dru757
Medical Policy Manual, Gender Affirming Interventions for Gender Dysphoria, Policy No. 153

Codes	**Number**	**Description**
HCPCS*	G0429	Dermal filler injection(s) to treat facial lipodystrophy syndrome (LDS)
	L8607	Injectable bulking agent for vocal cord medialization, 0.1ml
	J0591	Injection, Kybella, deoxycholic acid, 1 mg
	Q2026	Injection, Radiesse, 0.1 ml
	Q2028	Injection, Sculptra, 0.5mg

References

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Revision History

Revision Date	Revision Summary
9/19/2024	Added Prolaryn to list of products for review.
3/21/2024	New policy (effective 4/15/2024).

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Medication Policy Manual

Policy No: dru781

Topic: Lenmeldy, atidarsagene autotemcel

Date of Origin: July 15, 2024

Committee Approval Date: June 20, 2024

Next Review Date: 2025

Effective Date: July 15,2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Lenmeldy (atidarsagene autotemcel) is an intravenous (IV) gene therapy used to treat a rare lysosomal disease, metachromatic leukodystrophy (MLD).

Policy/Criteria

Most contracts require pre-authorization approval of Lenmeldy (atidarsagene autotemcel) prior to coverage.

I. Continuation of therapy (COT): Lenmeldy (atidarsagene autotemcel) may be considered medically necessary for COT when full policy criteria below are met, including quantity limit.

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment naïve): Lenmeldy (atidarsagene autotemcel) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A through D below are met.

A. A diagnosis of **metachromatic leukodystrophy** (MLD), has been established by a specialist in neurology or genetics.

AND

B. MLD diagnosis has been confirmed by meeting all of the following criteria (1, 2, and 3) below:

1. Arylsulfatase-A (ARSA) enzyme levels of < 10%.

AND

2. Genetic confirmation of ARSA mutation.

AND

3. A positive urinary analysis for the presence of sulfatides.

AND

C. Patient MLD subtype has been confirmed as one of the following (1, 2, or 3) below:

1. **Pre-symptomatic late-infantile (PSLI)** by having the absence of neurologic symptoms.

OR

2. **Pre-symptomatic early juvenile (PSEJ)** by having the absence of neurologic symptoms.

OR

3. **Early symptomatic early juvenile (ESEJ**) by meeting both of the following criteria (a and b):

a. Intelligence quotient of ≥ 70.

AND

b. Ability to walk independently for ≥ 10 steps.

AND

D. The patient is a suitable candidate for Lenmeldy (atidarsagene autotemcel) and meets all of the following criteria (1 through 4) below:

1. No prior history of hematopoietic stem cell therapy (HSCT).

AND

2. Patient is fit for therapy, as defined by meeting all the criteria (a and b) below.

a. The patient has adequate and stable kidney, liver, and cardiac function (provider attestation).

AND

b. The patient has no active systemic infections (including, but not limited to HCV, HBV, and HIV infection) (provider attestation).

AND

3. Treatment with HSCT is contraindicated (including, but not limited to lack of matched donor, comorbidities, and age.)

AND

4. The patient is less than 7 years of age at the time of infusion.

PLEASE NOTE: Suitability for therapy must be documented in recent clinical documentation (such as in chart notes, laboratory reports), which MUST include evaluation for HSCT [bone marrow transplant (BMT)].

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Lenmeldy (atidarsagene autotemcel) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Lenmeldy (atidarsagene autotemcel) may be authorized in quantities of one treatment course per lifetime.

C. Additional infusions of Lenmeldy (atidarsagene autotemcel) will not be authorized.

IV. Lenmeldy (atidarsagene autotemcel) is considered investigational when used for all other conditions, including, but not limited to:

A. Late juvenile MLD

B. Adult MLD

C. Patients 7 years of age or older

Position Statement

Summary

- Lenmeldy (atidarsagene autotemcel) is an approved intravenously (IV) administered gene therapy that uses a lentiviral vector to encode functional copies of the arylsulfatase-A (ARSA) gene into hematopoietic stem cells, allowing for adequate production of the ARSA enzyme.
- Lenmeldy (atidarsagene autotemcel) is a one-time IV infusion. However, it is a very complex, high-cost therapy and require several phases of administration, extended hospitalization, and extensive supportive care, similar to a HSCT.
- The intent of this policy is to allow for coverage of Lenmeldy (atidarsagene autotemcel) in patients with a confirmed diagnosis of early onset MLD, when prescribed by a specialist, who are clinically suitable to receive Lenmeldy (atidarsagene autotemcel), as detailed in the coverage criteria.
- Patients must be otherwise clinically stable and healthy enough to receive a hematopoietic stem cell transplant (HSCT).
- Current available evidence for Lenmeldy (atidarsagene autotemcel) is limited to an integrated analysis of two, small single-arm, non-randomized trials plus an expanded access program, that evaluated severe motor impairment-free survival and severe cognitive impairment across three subtypes of MLD, reporting the following efficacy results from the most recent data analysis:
    * Presymptomatic late-infantile (PSLI): 19/20 patients were free of severe motor and cognitive impairment compared to zero in the natural history trial.
    * Presymptomatic early juvenile (PSEJ): 3/6 evaluable patients maintained ambulation and cognition past the age for which decline would be expected.
    * Early symptomatic early juvenile (ESEJ): 4/8 evaluable patients had favorable cognitive outcomes in the setting of severe motor decline, not following the natural course of MLD disease progression.
    * However, due to an extremely small sample size and limited efficacy in the PSEJ and ESEJ subtypes, the long-term-clinically meaningful outcomes in these subtypes remain unclear.
- Prior to the approval of Lenmeldy (atidarsagene autotemcel), treatment of MLD was mainly supportive in nature with HSCT being the only guideline recommended treatment option with proven efficacy in patients with MLD. However, not all patients suffering from MLD are eligible for an HSCT due to an unmatched donor, age, or other comorbidities. For this specific population, the potential benefit of Lenmeldy (atidarsagene autotemcel) may outweigh the risks.
- At this time, there is insufficient evidence to establish the safety and efficacy in other settings, including other subtypes for MLD. Additional trials are ongoing.
- Lenmeldy (atidarsagene autotemcel) may be covered for up to one dose per lifetime. There is no data on the safety or efficacy of repeated doses.

Disease Background[1-4]

- Metachromatic leukodystrophy (MLD), is a rare, recessive lysosomal disorder, caused by a mutation in the arylsulfatase-A (ARSA) gene, leading to an accumulation of sulfatides, triggering myelin sheath destruction in the peripheral and central nervous system, resulting in progressive loss of motor function, cognition, and ultimately death.
- The clinical spectrum of MLD is broad and heterogenous with three distinct clinical subtypes, categorized by age of onset, with earlier onset associated with a more severe and rapid disease course.
    * Late infantile:50-60% of MLD, severest form, onset <30 months, life expectancy <5 years.
    * Juvenile: 20-30% of MLD, onset >30 months to 6 years (early juvenile), 7-16 (late juvenile), life expectancy 10-20 years.
    * Adult: 10-30% of MLD, onset ≥17 years of age, slowly progressive, life expectancy >20 years.
- Each subtype above is classified even further based on presence or absence of symptoms; presymptomatic, early symptomatic, and late symptomatic.
- Symptoms of MLD vary depending on subtype and include learning disabilities, behavioral difficulties, gait disturbances, peripheral neuropathy, seizures, developmental delay, and loss of communication, ambulation, and ability to swallow.

Clinical Efficacy

Lenmeldy (atidarsagene autotemcel)[1 2 4-6]

- The safety and efficacy of Lenmeldy (atidarsagene autotemcel) was established primarily from results of an integrated analysis of two small, non-randomized, single-arm, open-label trials plus an expanded access program (n=37), in pediatric patients with MLD.
    * Patients were <7 years of age, with biochemical and genetically confirmed MLD. PSLI and PSEJ patients were negative for symptoms and ESEJ patients were required to have an intelligence quotient (IQ) of ≥ 70 and the ability to walk independently for ≥ 10 steps.
    * In addition, all patients were clinically suitable for Lenmeldy (atidarsagene autotemcel) therapy (adequate organ function with no active infections). Patients with severe liver, renal, or cardiac dysfunction and those with a prior HSCT were excluded from trial enrollment.
    * The patients were divided based on subtype (PSLI, n=20; PSEJ, n=7; ESEJ, n=10) and then compared to a retrospective observational natural history trial (n=41) as well as untreated sibling comparators for efficacy analysis.
    * However, due to varying baseline MLD disease severity in the PSEJ and ESEJ subtypes across trials, the FDA evaluated efficacy only on an individual basis compared to medical literature and available sibling comparators for these subtypes.

    - The primary endpoint was severe motor impairment free survival (sMFS) defined as time from birth to first occurrence of loss of locomotion and loss of sitting without support at 18 months, a clinically meaningful endpoint for MLD.
    - Severe cognitive impairment and overall survival (OS) were key secondary endpoints, which are also clinically relevant measures for MLD.
- At the most recent available data cut-off, the efficacy results for each MLD subtype were reported:
    - PSLI: 19/20 (95%) had not progressed to severe motor or cognitive impairment, while all patients (n=28) of natural history trial with PSLI had. In addition, evaluable treated patients saw an increase in OS of 58% at 6 years of age.
    - PSEJ: 3 current evaluable patients (3 had insufficient length of treatment and 1 died), retained the ability to walk (ages 8-13.6) with none progressing to severe cognitive impairment, surpassing the history of untreated patients. None of the treated siblings had severe motor impairment compared to 50% (2 of 4) of those untreated. OS was not evaluated due to insufficient length of treatment.
    - ESEJ: 4 of 8 patients (2 died), reported favorable cognitive outcomes in the setting of severe motor decline (never before reported in MLD disease history), with only 2 treated patients progressing to severe cognitive impairment. No evidence has been shown for OS benefit in ESEJ patients to date.
- However, an extremely small sample size, durability of effect, lack of a true comparator group, and limited efficacy data in the PSEJ and ESEJ setting, limit the certainty.
- In the near future, additional follow up data is expected, further evaluating the durability and safety of Lenmeldy (atidarsagene autotemcel) in these and other MLD subtypes.
- At this time, the safety and efficacy of Lenmeldy (atidarsagene autotemcel) in MLD subtypes other than PSLI, PSEJ, and ESEJ or for use in patients ≥7 years of age is unknown. Therefore, the use of Lenmeldy (atidarsagene autotemcel) in any MLD subtype other than those listed in coverage criteria is considered investigational.

Clinical Guidelines/Standard of Care Treatment[3 7 8]

- The treatment of patients with MLD requires a multidisciplinary approach due to the number of complications associated with the disease.
- Current treatment approaches for patients with MLD are mainly supportive in nature, with the key components of symptomatic relief consisting of anti-epileptics, muscle relaxers, pain relief, and physical therapy.
- Currently, HSCT is the only proven disease modifying treatment for MLD. Patients with early juvenile MLD who are treated with an HSCT having reported better gross motor and language outcomes and lower MRI severity scores compared to those that are untreated.
- Both the American College of Medical Genetics and Hunter's Hope Leukodystrophy Care Network most recent guidelines recommend HSCT as a treatment option in patients with presymptomatic disease or early symptomatic disease only, as HSCT benefit in those with symptomatic or advanced disease are unlikely to benefit from treatment.

- However, the use of HSCT is limited by availability of matched donors for the stem cell donation and the clinical stability of the patient being treated (adequate organ function, age, etc.).

Safety[1 2 4 6]

- The most common grade ≥ 3 treatment-emergent adverse events (AEs) seen during pivotal trials with Lenmeldy (atidarsagene autotemcel) were febrile neutropenia, stomatitis, neutropenia, gastroenteritis, and vomiting.
- The AEs noted above are consistent with those typically seen with the myeloablative conditioning regimen used prior to the Lenmeldy (atidarsagene autotemcel) infusion.
- Long-term safety data is limited as these trials are still ongoing, they are of a small sample size with a short treatment duration in regard to a chronic disease such as MLD.
- Additional safety data is warranted regarding potential long-term toxicities that may be associated with this novel gene therapy for MLD, including the risk for malignancies.

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Revision History

Revision Date	Revision Summary
06/20/2024	New policy. Policy intent to allow for coverage of Lenmeldy (atidarsagene autotemcel) in patients with a confirmed diagnosis of early onset MLD, when prescribed by a specialist, who are clinically suitable to receive Lenmeldy (atidarsagene autotemcel).

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Medication Policy Manual | **Policy No:** dru784

Topic: Amtagvi, lifileucel | **Date of Origin:** July 15, 2024

Committee Approval Date: June 20, 2024 | **Next Review Date:** 2025

Effective Date: July 15, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Amtagvi (lifileucel) is an immunotherapy that is designed to target malignant melanoma. The immune cells, also referred to as tumor-infiltrating lymphocytes (TILs), are manufactured from an individual patient's tumor cells via a complex process, and then reinfused back into the patient after a chemotherapy conditioning regimen.

Policy/Criteria

Most contracts require pre-authorization approval of Amtagvi (lifileucel) prior to coverage.

I. Continuation of therapy (COT): Amtagvi (lifileucel) may be considered medically necessary when full policy criteria below are met, including quantity limit. However, Amtagvi (lifileucel) is not coverable for repeated doses and is not coverable if a patient has previously received prior tumor-infiltrating lymphocyte (TIL) therapy.

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Amtagvi (lifileucel) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A, B, C, and D below are met:

A. A diagnosis of **cutaneous melanoma**, locally advanced (unresectable) or metastatic.

AND

B. There has been disease progression on or after the following (1 and 2):

1. An anti-programmed death receptor-1 (PD-1)-based regimen (as listed in *Appendix 1*)

AND

2. ***For BRAF V600 mutation-positive tumors:*** A combination BRAF/MEK inhibitor therapy. (see to *Appendix 2*)

AND

C. Suitability for Amtagvi (lifileucel) therapy as defined by all of the following (1 through 4):

Note: Suitability for Amtagvi (lifileucel) must be documented in recent clinical documentation (such as chart notes, laboratory reports).

1. The patient does not have untreated or active brain metastases.

AND

2. The patient has an ECOG performance status of 0 or 1. (*Appendix 3*)

AND

3. The patient has adequate and stable kidney, liver, and cardiac function (provider attestation).

AND

4. The patient has no active systemic infections [including, but not limited to HCV, HBV, and HIV infection] (provider attestation).

AND

D. No prior use of tumor-infiltrating lymphocyte (TIL) therapy.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy services considers Amtagvi (lifileucel) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Amtagvi (lifileucel) will be authorized in quantities of one-time treatment course per lifetime.

IV. Investigational Uses:

A. Repeat doses of Amtagvi (lifileucel), including for Amtagvi (lifileucel) previously given as part of a clinical trial.

B. Amtagvi (lifileucel) is considered investigational for all other conditions not specifically addressed in the coverage criteria defined above.

PLEASE NOTE: Any products not specifically addressed in this policy will be considered investigational.

Position Statement

Summary

- Amtagvi (lifileucel) is a tumor-derived autologous T-cell immunotherapy. The immune cells, or tumor-infiltrating lymphocytes (TILs), are designed to attack malignant melanoma cells. The manufacture and administration of this product is a complex process.
- Amtagvi (lifileucel) is indicated for the treatment of adults with unresectable or metastatic cutaneous melanoma that has previously been treated with a PD-1 blocking antibody [e.g., Opdivo (nivolumab), Keytruda (pembrolizumab)] and, if the tumor is BRAF V600 mutation-positive, a BRAF inhibitor either with or without a MEK inhibitor (see *Appendix 2*).
- The intent of this policy is to allow for coverage of Amtagvi (lifileucel) for unresectable or metastatic cutaneous melanoma when disease has progressed after standard-of-care front-line therapies and the patient is found fit to receive this intensive therapy regimen, as specified in the coverage criteria above.
- The approval of Amtagvi (lifileucel) is based on low-quality evidence from a single-arm, open-label study (no randomization, blinding, or comparator) that evaluated tumor response rate, an unvalidated surrogate endpoint, as the primary endpoint. The study included patients with unresectable or metastatic (stage IIIC or IV) cutaneous melanoma that had progressed after treatment with a PD-1 inhibitor and a BRAF inhibitor or BRAF plus MEK inhibitor if BRAF V600 mutation-positive.
- Because this is an intensive therapy involving lymphodepleting chemotherapy and infusion of Proleukin (aldesleukin), patients must be determined to be sufficiently fit. This includes careful assessment of performance status, organ function, and infection status. In addition, patients with untreated or active brain metastases were excluded from the pivotal clinical trial.

- Serious side effects, including death, have been reported with Amtagvi (lifileucel). Boxed warnings include treatment-related mortality, prolonged severe cytopenia, severe infection, cardiopulmonary disorders, and renal impairment. Administration is done in an inpatient setting with access to an intensive care facility and specialists who are skilled in cardiopulmonary or intensive care medicine.
- The National Comprehensive Cancer Network (NCCN) recommendation for Amtagvi (lifileucel) parallels the FDA indication. The guideline states that it should not be used if the patient has poor performance status, inadequate organ function, or untreated or active brain metastases.
- Amtagvi (lifileucel) was studied, and FDA approved as a one-time treatment in the dose listed in the package label. Use beyond a single treatment is considered investigational.
- The safety and effectiveness of Amtagvi (lifileucel) have not been adequately studied in other disease settings. Therefore, use in settings other than that which is described above are considered investigational.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Background [1,2]

- Amtagvi (lifileucel) is made from tumor-infiltrating lymphocytes (TILs) harvested from a patient's tumor. Patients who are not able to undergo surgery or patients from whom an adequate amount tumor tissue cannot be harvested are not eligible for this therapy.
- The turnaround time for the manufacture of Amtagvi (lifileucel) is approximately 34 days, not including time for shipment. The long wait time may be an issue for some patients.
- Prior to administration of Amtagvi (lifileucel), patients are pretreated with lymphodepleting chemotherapy for 7 days. After the Amtagvi (lifileucel) infusion,

Proleukin (aldesleukin) is administered every 8 to 12 hours for up to six doses. This therapy needs to be given in an inpatient hospital setting with access to an intensive care facility and specialists who are skilled in cardiopulmonary or intensive care medicine.

Clinical Efficacy *[2,3]*

- Efficacy was evaluated in a single-arm study [Study C-144-01] in 73 patients who received Amtagvi (lifileucel) for their unresectable or metastatic (stage IIIC or IV) cutaneous melanoma. *This is an FDA accelerated approval.*
    * Patients enrolled in the study had at least one prior systemic therapy, which must have included a PD-1 blocking antibody and, if BRAF V600 mutation-positive, a BRAF/MEK inhibitor therapy. The median number of prior lines of systemic therapy in the study population was three (range 1 to 8).
    * All patients had prior PD-1 inhibitor therapy, 86% had prior anti-CTLA-4 therapy [e.g., Yervoy (ipilimumab)], 58% had combination PD-1 inhibitor/anti-CTLA-4 therapy, and 27% had prior BRAF or BRAF+MEK inhibitor therapy.
    * All patients were required to have good performance status (EGOC PS of 0 or 1), acceptable hematologic parameters, and adequate organ function.
    * Patients with uncontrolled or symptomatic brain metastasis, ocular or uveal melanoma, an organ allograft, or prior cell transfer therapy were not included in the study.
    * Amtagvi (lifileucel) administration was preceded by a seven-day lymphodepleting course of chemotherapy and was followed by a six-dose course of Proleukin (aldesleukin).
    * Tumor response was the primary endpoint. The overall response rate was 32% with 4% complete responses. The median duration of response was not reached; however, 57% of patients were still responding at $\geq$6 months and 44% at $\geq$12 months.
- The quality of the evidence for Amtagvi (lifileucel) is poor. The study was not controlled (no comparator group) nor blinded so there is a great potential for bias. Additionally, tumor response has not been shown to be an accurate predictor of important clinical outcomes such as improved overall survival or quality of life. Additional, higher quality evidence is needed before it can be determined whether the benefit of Amtagvi (lifileucel) outweighs the significant harms associated with its use.

Guidelines *[4]*

- The National Comprehensive Cancer Network (NCCN) cutaneous melanoma guideline lists Amtagvi (lifileucel) among its recommendations for second- or subsequent-line treatment of metastatic or unresectable cutaneous melanoma after therapy with a PD-1 inhibitor therapy and, if the tumor is BRAF V600 mutation-positive, a BRAF and MEK inhibitor combination. Amtagvi (lifileucel) should not be used in patients with poor performance status, inadequate organ function, or untreated or active brain metastases.

Investigational and Other Uses [5]

- Amtagvi (lifileucel) has not been studied in cancer settings other than that which is described in the coverage criteria described in this policy. Any use outside of this setting (subsequent-line treatment of unresectable or metastatic cutaneous melanoma) is considered investigational.

Safety [1,2]

- Serious adverse effects (AEs) including death, have occurred after infusion of Amtagvi (lifileucel). Refer to package labeling for guidance on its use.
- Boxed warnings include treatment-related mortality, prolonged severe cytopenia, severe infection, cardiopulmonary disorders, and renal impairment.

Dosing and Administration [1]

- Amtagvi (lifileucel) is administered as a single intravenous dose of tumor-derived T-cells containing 7.5×10^9 to 72×10^9 viable cells (for autologous use only).
- The turnaround time for the manufacture of Amtagvi (lifileucel) is approximately 34 days, not counting time for shipment.
- Prior to infusion, patients are pretreated with lymphodepleting chemotherapy for seven days. Infusion of lifileucel should be as soon as possible after 24 hours have elapsed following the final chemotherapy (fludarabine) infusion, but no later than 4 days.
- Beginning 3 to 24 hours after the lifileucel infusion, aldesleukin is administered every 8 to 12 hours for up to 6 doses.
- Amtagvi (lifileucel) needs to be administered in an inpatient hospital setting with access to an intensive care facility and specialists who are skilled in cardiopulmonary or intensive care medicine.
- Treatment with Amtagvi (lifileucel) is only available through select treatment centers authorized by the manufacturer. Refer to: https://www.amtagvi.com/support-and-resources/authorized-treatment-center/
- In some regions, site of care may be further limited by providers.

Appendix 1: FDA-Approved PD-1 and PD-L1 Blocking Monoclonal Antibody Therapies [a]
Programmed death receptor-1 (PD-1) inhibitors
Jemperli (dostarlimab)
Keytruda (pembrolizumab
Libtayo (cemiplimab)
Loqtorzi (toripalimab)
Opdivo (nivolumab)
Tevimbra (tislelizumab)
Zynyz (retifanlimab)
Programmed death receptor-1 (PD-1) inhibitors
Bavencio (avelumab)
Imfinzi (durvalumab)
Tecentriq (atezolizumab)

[a] Or as listed on the FDA.gov website

Appendix 2: FDA-Approved BRAF/MEK Combination therapies for BRAF V600 Mutation-Positive Melanoma [a]
Braftovi (encorafenib) plus Mektovi (binimetinib)
Tafinlar (dabrafenib) plus Mekinist (trametinib)
Zelboraf (vemurafenib) plus cobimetinib (Cotellic)

[a] Or as listed on the FDA.gov website

Appendix 3: Eastern Cooperative Oncology Group (ECOG) Performance Status Definitions	
Grade	***Definition***
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

Cross References
BRAF inhibitors, Medication Policy Manual, Policy No. dru728
Mitogen-activated extracellular signal-regulated kinase (MEK) inhibitors, Medication Policy Manual, Policy No. dru727
Opdivo, nivolumab, Medication Policy Manual, Policy No. dru390
Keytruda, pembrolizumab, Medication Policy Manual, Policy No. dru367
Yervoy, ipilimumab, Medication Policy Manual, Policy No. dru238

Codes	Number	Description
HCPCS	J9999	Not otherwise classified, antineoplastic drugs
HCPCS	J3590	Unclassified biologics

References

1. Amtagvi™ (lifileucel) [package insert]. Iovance Biotherapeutics Manufacturing LLC; Philadelphia, PA; February 2024.
2. Center for Drug Evaluation and Research; U.S. Food and Drug Administration BLA Clinical Review and Evaluation, BLA 125773; Amtagvi (lifileucel). [cited 3/18/2024]. Available from: https://www.fda.gov/vaccines-blood-biologics/approved-blood-products/amtagvi.
3. Chesney J, Lewis KD, Kluger H, et al. Efficacy and safety of lifileucel, a one-time autologous tumor-infiltrating lymphocyte (TIL) cell therapy, in patients with advanced melanoma after progression on immune checkpoint inhibitors and targeted therapies: pooled analysis of consecutive cohorts of the C-144-01 study. J Immunother Cancer. England, 2022.
4. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology™. [Updated routinely]. [cited with policy updates and as necessary]. Available from: https://www.nccn.org/guidelines/category_1.
5. National Institutes of Health, Clinicaltrials.gov [website]. [cited periodically]. Available from: www.clinicaltrials.gov.

Revision History

Revision Date	Revision Summary
6/20/2024	New policy (effective 7/15/2024). - Limits coverage of Amtagvi (lifileucel) to patients with unresectable or metastatic cutaneous melanoma who have had prior treatment with a PD-1 inhibitor antibody and, if BRAF V600 mutation-positive, BRAF or BRAF/MEK inhibitor therapy. - Patients must be determined to be suitable to receive therapy with Amtagvi (lifileucel) including adequate performance status, adequate organ function, no untreated or active brain metastases, and no active systemic infections. - Use beyond one treatment per lifetime is considered investigational. - All other uses are considered investigational.

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Medication Policy Manual

Policy No: dru785

Topic: Tevimbra, tislelizumab-jsgr

Date of Origin: July 15, 2024

Committee Approval Date: June 20, 2024

Next Review Date: 2025

Effective Date: July 15, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Tevimbra (tislelizumab) is an intravenously administered immunotherapy used in the management of specific types of cancer [such as esophageal squamous cell carcinoma (ESCC)]. It belongs to a class of medications called programmed death receptor-1 (PD-1) blocking antibodies.

Policy/Criteria

Most contracts require pre-authorization approval of Tevimbra (tislelizumab) prior to coverage.

I. Continuation of therapy (COT): Tevimbra (tislelizumab) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Tevimbra (tislelizumab) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A, B, C, and D below are met:

A. A diagnosis of **esophageal squamous cell carcinoma (ESCC)**, locally advanced (unresectable) or metastatic.

AND

B. Disease progression on or after at least one prior systemic therapy for advanced disease (locally advanced or metastatic). [Note: This includes disease recurring within 6 months of completing neoadjuvant or neoadjuvant chemotherapy]

AND

C. Tevimbra (tislelizumab) will be used as monotherapy.

AND

D. No prior programmed death receptor-1 (PD-1) blocking antibody (PD-1 inhibitor) or programmed death-ligand 1 (PD-L1) blocking antibody (PD-L1 inhibitor) therapy (see *Appendix 1*).

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy services considers Tevimbra (tislelizumab) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Tevimbra (tislelizumab) will be authorized in doses up to 200 mg every three weeks until disease progression.

C. Authorization **may** be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement, and lack of disease progression based on an assessment of change in tumor burden.

IV. Tevimbra (tislelizumab) is considered not medically necessary when used as an add-on to chemotherapy for first-line treatment of locally advanced (unresectable) or metastatic ESCC.

V. Tevimbra (tislelizumab) is considered investigational when used for all other conditions including, but not limited to, esophageal adenocarcinoma.

Position Statement

Summary

- Tevimbra (tislelizumab) is an intravenously administered programmed death receptor-1 (PD-1) blocking antibody. It is indicated as a single agent for the treatment of adult patients with locally advanced (unresectable) or metastatic esophageal squamous cell carcinoma (ESCC). It is the third PD-1 inhibitor approved in this treatment setting.
- The intent of this policy is to allow for coverage of Tevimbra (tislelizumab) when used as a single agent for locally advanced (unresectable) or metastatic ESCC that has recurred or progressed after prior standard-of-care chemotherapy.
- The use of Tevimbra (tislelizumab) after disease progression on prior immune checkpoint inhibitor therapy (e.g., PD-1 or PD-1 inhibitors) has not been evaluated.
- The approval of Tevimbra (tislelizumab) as a second- or subsequent-line therapy for locally advanced (unresectable) or metastatic ESCC is based on evidence from a randomized controlled trial which demonstrated an overall survival advantage for Tevimbra (tislelizumab) relative to single-agent chemotherapy.
- Esophageal cancer is classified as having either squamous cell carcinoma (ESCC) or adenocarcinoma histology. Tevimbra (tislelizumab) has only been evaluated in ESCC.

- Tevimbra (tislelizumab) has also been evaluated as an add-on to front-line chemotherapy in first-line treatment of locally advanced (unresectable) or metastatic ESCC; however, unlike Opdivo (nivolumab) and Keytruda (pembrolizumab), it is not FDA-approved in this setting. Although all three PD-1/PD-L1 inhibitor therapies appear similar with respect to safety and efficacy, the relative cost of Tevimbra (tislelizumab) is not available; therefore, Tevimbra (tislelizumab) is currently considered 'not medically necessary' in the front-line setting for advanced ESCC.
- As with other PD-1/PD-L1 inhibitor therapies, the primary adverse effects of concern with Tevimbra (tislelizumab) are immune-mediated toxicities (e.g., endocrinopathies, colitis, hepatitis).
- At this time, the National Comprehensive Cancer Network (NCCN) guidelines do not yet include recommendations for Tevimbra (tislelizumab). Opdivo (nivolumab), Keytruda (pembrolizumab), and single-agent chemotherapy are listed among the preferred recommendations for locally advanced or metastatic ESCC that has progressed after prior systemic therapy.
- Tevimbra (tislelizumab) was studied, and FDA approved, in the doses listed in the product prescribing information. Use of doses or frequencies exceeding these quantities are considered investigational.
- The safety and effectiveness of Tevimbra (tislelizumab) have not been adequately studied in other disease settings. Therefore, use in settings other than that which is described in the coverage criteria above are considered investigational.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Background [1]

- Esophageal cancers are classified by histology as either squamous cell carcinoma (ESCC) or adenocarcinoma.
- There are differences in the treatment pathways based on disease histology. At this time, Tevimbra (tislelizumab) has only been studied in ESCC.

Clinical Efficacy

- *Subsequent therapy*: The efficacy of Tevimbra (tislelizumab) as a single agent in recurrent (previously treated) locally advanced (unresectable) or metastatic esophageal squamous cell carcinoma (ESCC) was evaluated in a randomized controlled trial (RCT) where it was compared with single-agent chemotherapy [RATIONALE-302 Study; N=512]. [2]
    * Patients enrolled in the study had disease progression on or after prior systemic therapy in the advanced or metastatic disease setting. The study also included patients whose disease recurred within 6 months of completing a course of neoadjuvant or adjuvant chemotherapy or chemoradiotherapy.
    * Patients with active brain metastases, histology other than ESCC, or who had prior PD-1/PD-L1 inhibitor therapy were excluded from the study.
    * The study compared Tevimbra (tislelizumab) 200 mg IV every 3 weeks versus investigator's choice of single agent chemotherapy (paclitaxel, docetaxel, or irinotecan).
    * Median overall survival (OS) was 8.6 months and 6.3 months in the Tevimbra (tislelizumab) and chemotherapy treatment arms, respectively. This is a statistically significant difference.
- *First-line therapy*: A second RCT [RATIONALE-306; N=649] studied Tevimbra (tislelizumab) as an add-on to standard front-line chemotherapy in patients with locally advanced (unresectable) or metastatic ESCC where it was compared with placebo plus standard front-line chemotherapy. [3] *Tevimbra (tislelizumab) is not currently FDA-approved in this setting.*
    * The study enrolled patients who had no prior therapy for their locally advanced or metastatic ESCC and the disease was not amenable to definitive therapies (curative intent) including surgery and radiation. If patients had received prior neoadjuvant or adjuvant platinum-based chemotherapy, a treatment-free interval (no disease progression) of at least 6 months was required.
    * Patients with active brain metastases, histology other than ESCC, or who had prior PD-1/PD-L1 inhibitor therapy were excluded from the study.
    * The study compared Tevimbra (tislelizumab) plus a platinum doublet with placebo plus a platinum doublet. The platinum (cisplatin or oxaliplatin) was stopped after six cycles. Tevimbra (tislelizumab) was continued until disease progression.
    * An OS benefit was observed with Tevimbra (tislelizumab) relative to placebo with median OS of 17.2 months and 10.6 months, respectively.

* Both Opdivo (nivolumab) and Keytruda (pembrolizumab) are already FDA approved in this first-line treatment setting. However, unlike Opdivo (nivolumab) and Keytruda (pembrolizumab), Tevimbra (tislelizumab)is not FDA-approved in this setting. Although there is no directly comparative evidence, all three PD-1/PD-L1 inhibitor therapies appear similar with respect to safety and efficacy. However, the relative cost of Tevimbra (tislelizumab) is not yet available. As the clinical value of Tevimbra (tislelizumab) cannot yet be calculated, Tevimbra (tislelizumab) is considered 'not medically necessary' in the front-line setting for advanced ESCC as there are similar alternatives.

Guidelines [1]

- The National Comprehensive Cancer Network (NCCN) Esophageal Cancer guideline lists the following as preferred, category 1 recommendations for unresectable locally advanced, recurrent, or metastatic ESCC:
  * ***Front-line:*** The combination of a fluoropyrimidine and a platin (cisplatin or oxaliplatin) plus Opdivo (nivolumab) OR a fluoropyrimidine and cisplatin plus Keytruda (pembrolizumab). Keytruda (pembrolizumab) is only recommended for tumors with PD-L1 CPS $\geq$10.
  * ***Second- and subsequent-line:*** Single agent Opdivo (nivolumab), Keytruda (pembrolizumab), or Tevimbra (tislelizumab); OR single agent docetaxel, paclitaxel, or irinotecan. Keytruda (pembrolizumab) is only recommended for tumors with PD-L1 CPS $\geq$10.
  * The use of PD-1 inhibitors [such as Opdivo (nivolumab) or Keytruda (pembrolizumab)] is only recommended if there has been no prior tumor progression on checkpoint inhibitor therapy (e.g., PD-1 or PD-L1 inhibitor).

Investigational and Other Uses [3,4]

- Tevimbra (tislelizumab) is currently being studied in several other types of cancers including non-small cell lung cancer (NSCLC), squamous cell cancer of the head and neck (SCCHN), ovarian cancer, and gastric cancer. However, to date, Tevimbra (tislelizumab) has not been shown to be an effective therapy for these cancers.

Safety [5]

- The primary adverse effects (AEs) of interest for Tevimbra (tislelizumab) include immune-mediated reactions and infusion reactions. Immune-related AEs can affect any organ system or tissue (e.g., colitis, pneumonitis, hepatitis, endocrinopathies, nephritis with renal dysfunction, and dermatologic reactions).
- Overall, the safety of Tevimbra (tislelizumab) appears to be similar to other PD-1 and PD-L1 inhibitors.

Dosing [5]

- Tevimbra (tislelizumab) is given via intravenous infusion over 30 to 60 minutes.
- Tevimbra (tislelizumab) is given as a single agent in a dose of 200 mg every three weeks. It is administered until disease progression.

Appendix 1: FDA-Approved PD-1 and PD-L1 Blocking Monoclonal Antibody Therapies [a]
Programmed death receptor-1 (PD-1) inhibitors
Jemperli (dostarlimab)
Keytruda (pembrolizumab
Libtayo (cemiplimab)
Loqtorzi (toripalimab)
Opdivo (nivolumab)
Tevimbra (tislelizumab)
Zynyz (retifanlimab)
Programmed death receptor-1 (PD-1) inhibitors
Bavencio (avelumab)
Imfinzi (durvalumab)
Tecentriq (atezolizumab)

[a] Or as listed on the FDA.gov website

Cross References
Opdivo, nivolumab, Medication Policy Manual, Policy No. dru390
Keytruda, pembrolizumab, Medication Policy Manual, Policy No. dru367

Codes	Number	Description
HCPCS	J3490	Unclassified drugs

References

1. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology™. [Updated routinely]. [cited with policy updates and as necessary]. Available from: https://www.nccn.org/guidelines/category_1.
2. Shen L, Kato K, Kim SB, et al. Tislelizumab Versus Chemotherapy as Second-Line Treatment for Advanced or Metastatic Esophageal Squamous Cell Carcinoma (RATIONALE-302): A Randomized Phase III Study. J Clin Oncol. United States, 2022:3065-76.
3. Xu J, Kato K, Raymond E, et al. Tislelizumab plus chemotherapy versus placebo plus chemotherapy as first-line treatment for advanced or metastatic oesophageal squamous cell carcinoma (RATIONALE-306): a global, randomised, placebo-controlled, phase 3 study. *Lancet Oncol.* 2023;24(5):483-95. PMID: 37080222
4. National Institutes of Health, Clinicaltrials.gov [website]. [cited periodically]. Available from: www.clinicaltrials.gov.
5. Tevimbra® (tislelizumab-jsgr) [package insert]. BeiGene USA, Inc.; San Mateo, CA; March 2024.

Revision History

Revision Date	Revision Summary
6/20/2024	New policy (effective 7/15/2024). - Limits coverage of Tevimbra (tislelizumab) as a single agent for patients with locally advanced (unresectable) or metastatic esophageal squamous cell carcinoma (ESCC) when disease has progressed on at least on prior systemic therapy. - Use is limited to patients who have not received prior PD-1/PD-L1 therapy. - Use in combination with front-line chemotherapy is considered not medically necessary. - All other uses are considered investigational.

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Medication Policy Manual | **Policy No:** dru791

Topic: Anktiva, nogapendekin alfa inbakicept | **Date of Origin:** December 1, 2024

Committee Approval Date: December 12, 2024 | **Next Review Date:** 2025

Effective Date: March 1, 2025

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Anktiva (nogapendekin alfa inbakicept) is an intravesically administered (instilled into the bladder via a catheter and retained for two hours) interleukin-15 (IL-15) receptor agonist approved for use in combination with Bacillus Calmette-Guérin (BCG) for adults with BCG-unresponsive non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS).

Policy/Criteria

Most contracts require pre-authorization approval of Anktiva (nogapendekin alfa inbakicept) prior to coverage.

I. Continuation of therapy (COT): Anktiva (nogapendekin alfa inbakicept) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Anktiva (nogapendekin alfa inbakicept) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A through E below are met:

A. A diagnosis of **non-muscle invasive bladder cancer (NMIBC) with carcinoma *in situ* (CIS)** either with or without papillary tumors.

AND

B. The tumor is Bacillus Calmette-Guérin (BCG)-unresponsive as defined by the following (1 or 2):

1. Persistent or recurrent CIS alone after adequate BCG therapy (refer to *Appendix 1*)

OR

2. Recurrent Ta/T1 disease within 12 months of BCG therapy.

AND

C. The patient is ineligible or has elected not to undergo a cystectomy (removal of the bladder).

AND

D. Treatment with each of the following was not tolerated or is contraindicated (1 and 2):

1. Keytruda (pembrolizumab)

AND

2. Adstiladrin (nadofaragene firadenovec).

AND

E. Anktiva (nogapendekin alfa inbakicept) will be administered in combination with Bacillus Calmette-Guerin (BCG).

III. Administration, Quantity Limitations (QL), and Authorization Period

A. Regence Pharmacy Services considers Anktiva (nogapendekin alfa inbakicept) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Anktiva (nogapendekin alfa inbakicept) may be approved in quantities and time periods as follows in *Table 1*:

Table 1. Anktiva (nogapendekin alfa inbakicept) QL Authorization per Dosing Phase:

Dosing Phase	**Doses / Time period** (authorization duration)	**Notes**
Initial Induction	Weeks 0 to 12 (6 doses/ 3 months)	If CR at Month 3, proceed to *Initial Maintenance*.
Second Induction [a]	Weeks 13 to 24 (6 doses / 3 months)	If CR to *Second Induction* after 3 months, proceed to *Initial Maintenance* ('restart the clock' to Month 4)
Initial Maintenance (dosed every 3rd month)	Month 4-6 and Month 7-9 (6 doses / 6 months)	Dosing in Month 4 and Month 7 only
	Month 10-12 and Month 13-18 (6 doses / 6 months)	Dosing in Month 10 and Month 13 only
Ongoing maintenance (dosed every 6th month)	Month 19-24 (3 doses/ 6 months)	Dosing in Month 19 only
	Month 25-30 (3 doses / 6 months)	Dosing in Month 25 only
	Month 31-36 (3 doses / 6 months)	Dosing in Month 31 only
	Month 37 (3 doses / 1 month)	Dosing in Month 37 only

CR: complete response

[a] Second Induction is coverable only if no complete response at Month 3 with Initial Induction. After Second Induction, subsequent authorization will be per Initial Maintenance.

C. Re-authorization: Authorization **shall** be reviewed at least every 6 months (or as listed in *Table 1* above) to confirm current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met. Specifically, documentation that the medication is providing clinical benefit, including disease stability or improvement, and lack of disease progression, based on an assessment of change in tumor burden. If there is documentation of potential disease progression, a shortened authorization (up to three months) may be approved to allow time for clarification of response to Anktiva (nogapendekin alfa inbakicept), including clinical re-evaluation of the patient and assessment of tumor status.

PLEASE NOTE: Additional doses of Anktiva (nogapendekin alfa inbakicept) will not be authorized without a documented recent assessment by the treating provider (such as a urologist or oncologist) with objective evidence of response to therapy, such as by cystoscopy, biopsy, urine cytology, or other imaging ("restaging scans").

IV. Anktiva (nogapendekin alfa inbakicept) is considered investigational when used for all other conditions.

Position Statement

Summary

- Anktiva (nogapendekin alfa inbakicept) is an interleukin-15 (IL-15) receptor agonist that is administered via instillation into the bladder through a urinary catheter. It exerts anti-tumor activity through its activation and proliferation of natural killer (NK), CD8+, and memory T cells.
- Anktiva (nogapendekin alfa inbakicept) is indicated in combination with Bacillus Calmette-Guerin (BCG) for the treatment of non-muscle invasive bladder cancer (NMIBC) with carcinoma *in situ* (CIS), either with or without papillary tumors, that was unresponsive to prior therapy with BCG.
- The purpose of this policy is to allow for coverage of Anktiva (nogapendekin alfa inbakicept) for NMIBC with CIS in patients who were unresponsive to prior therapy with BCG when patients are ineligible for or have elected not to undergo cystectomy and therapy with both Keytruda (pembrolizumab) and Adstiladrin (nadofaragene firadenovec) was not tolerated or is contraindicated.
- The approval of Anktiva (nogapendekin alfa inbakicept) was based on evidence from a single-arm, observational study that evaluated tumor response in patients with BCG-unresponsive, high-risk, NMIBC with CIS. Sixty-two percent of patients were considered to have complete response at any time during their treatment.
- Tumor response is an unvalidated surrogate endpoint. There is currently no evidence that Anktiva (nogapendekin alfa inbakicept) provides any clinically meaningful benefit such as improved symptom control or improved overall survival.
- Both Keytruda (pembrolizumab) and Adstiladrin (nadofaragene firadenovec) are also approved for use in BCG-unresponsive NMIBC with CIS based on a similar level of evidence. Anktiva (nogapendekin alfa inbakicept) has not been compared with these or with any other NMIBC therapies.
- Anktiva (nogapendekin alfa inbakicept) has not been shown to be safer or more effective than other therapies for BCG-unresponsive NMIBC with CIS; however, it is the most costly.
- Like other systemic and intravesical administered therapies for NMIBC with CIS, Anktiva (nogapendekin alfa inbakicept) labeling contains a warning that delaying cystectomy (removal of the bladder) can lead to the development of metastatic bladder cancer which can be lethal.
- The National Comprehensive Cancer Network (NCCN) bladder cancer guideline lists Anktiva (nogapendekin alfa inbakicept), Keytruda (pembrolizumab) and Anktiva (nogapendekin alfa inbakicept) as treatment options for BCG-unresponsive NMIBC with CIS.
- Anktiva (nogapendekin alfa inbakicept) was studied and FDA approved in the doses listed in the product prescribing information. Use of doses or frequencies exceeding these quantities are considered investigational.
- The safety and effectiveness of Anktiva (nogapendekin alfa inbakicept) have not been adequately studied in other disease settings. Therefore, use in settings other than that which is described above are considered investigational.
- *Reauthorization Criteria*: When coverage criteria are met, Anktiva (nogapendekin alfa inbakicept) is authorized for six months (24 weeks) of therapy, after which time

documentation must be provided to establish that the medication is effective. Specifically, there must be documentation of clinical benefit, including disease stability or improvement and there is a lack of disease progression, based on an assessment of change in tumor burden. Documentation of benefit must include the most recent objective assessment of tumor status, which may include cystoscopy, biopsy, urine cytology, or other imaging ("restaging scans") by the treating urologist (or oncologist). Given the complexity of the evaluation, including use of the criteria, Anktiva (nogapendekin alfa inbakicept) will not be reauthorized without an assessment of response to therapy, such a partial response (PR), complete response (CR), or stable disease (SD).

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Background *[1 2]*

- Approximately 10% of non-muscle invasive bladder cancer (NMIBC) cases are classified as carcinoma in situ (CIS). CIS is a high-grade tumor confined to the urothelial layer of the bladder. CIS is prone to recurrence and progression to invasive disease and metastasis.
- Management of NMIBC is aimed at reducing disease recurrence and preventing progression to more advanced stages.

Clinical Efficacy *[2 3]*

- The efficacy of Anktiva (nogapendekin alfa inbakicept) is based on a low-quality, single-arm study [QUILT-3.032] in patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk NMIBC with CIS that evaluated tumor response as the primary endpoint.

    * Enrolled patients all had NMIBC with CIS. Patients with a diagnosis of NMIBC with CIS and Ta/T1 papillary disease were also allowed to participate.
    * BCG-unresponsive disease was defined as persistent or recurrent CIS alone or with Ta/T1 (papillary) disease within 12 months of adequate BCG therapy. Adequate BCG therapy was defined as a minimum of 5 of 6 doses of an initial induction course plus either 1) at least 2 of 3 doses of maintenance therapy, or 2) at least 2 of 6 doses of a second induction course.
    * Sixty-two percent of patients in the study had a complete response at any time during the study, and 58% of patients had continued response at 12 months or more.
    * Tumor response has not been shown to accurately predict improvement in any clinically important outcome (e.g., improved quality of life or overall survival). A median of 12 doses of Anktiva (nogapendekin alfa inbakicept) was received by patients over the course of the study.
- Keytruda (pembrolizumab) and Adstiladrin (nadofaragene firadenovec) have also been evaluated and are approved for use in BCG-unresponsive high-risk NMIBC with CIS. The evidence for all three therapies is of similar quality (single-arm trials that evaluate tumor response as a surrogate endpoint). [3-5] There is no evidence directly comparing any of these therapies.

Guidelines *[1]*

- The National Comprehensive Cancer Network (NCCN) bladder cancer guideline lists cystectomy (removal of the bladder) as the preferred therapy for BCG-unresponsive or -intolerant NMIBC. Intravesical administration of chemotherapy (e.g., gemcitabine, mitomycin), Adstiladrin (nadofaragene firadenovec), Anktiva (nogapendekin alfa inbakicept), and systemic Keytruda (pembrolizumab) are also listed as potential therapy options.

Reauthorization Criteria**:**

- When coverage criteria are met, Anktiva (nogapendekin alfa inbakicept) is authorized for six months (24 weeks) of therapy, after which time documentation must be provided to establish that the medication is effective. Specifically, there must be documentation of clinical benefit, including disease stability or improvement and there is a lack of disease progression, based on an assessment of change in tumor burden.
    * Criteria used for assessment of response to therapy for cancer varies, depending on the tumor type and the therapy. Per the pivotal trial protocol of Anktiva (nogapendekin alfa inbakicept), progression was defined as presence or development of any of the following: [6]
        - Development of (including recurrence of) or increase in stage to: Lamina propria invasion (e.g., recurrence of T1; increase from Ta to T1 or carcinoma in situ (CIS) to T1)
        - Muscle-invasive disease (stage ≥ T2)
        - Lymph node (N+) or distant metastasis (M1)
        - Increase in grade from low to high (including CIS)

    * Documentation of benefit must include the most recent objective assessment of tumor status, which may include cystoscopy, biopsy, urine cytology, or other imaging ("restaging scans") by the treating urologist (or oncologist). Given the complexity of the evaluation, including use of the criteria, Anktiva (nogapendekin alfa inbakicept) will not be reauthorized without an assessment of response to therapy, such a partial response (PR), complete response (CR), or stable disease (SD).
    * If there is documentation of potential disease progression ["unconfirmed progressive disease (UPD)"], a shortened authorization (up to three months) may be approved to allow time for clarification of response to Anktiva (nogapendekin alfa inbakicept), including clinical re-evaluation of the patient and an assessment of change in tumor burden, which may include cystoscopy, biopsy, and urine cytology.
- If a patient has confirmed, unequivocal new lesions (progression of disease, PD), additional Anktiva (nogapendekin alfa inbakicept) is not coverable. If a new lesion is equivocal, UPD reassessment by the treating oncologist with repeat assessment of tumor burden would apply (as noted above).

Investigational and Other Uses

- Use of Anktiva (nogapendekin alfa inbakicept) in any setting other than that listed under coverage criteria in Section II. is considered investigational.

Safety *[3-5]*

- Most adverse effects from Anktiva (nogapendekin alfa inbakicept) are local and include dysuria, hematuria, urinary frequency or urgency, and urinary tract infections.
- Systemic side effects may include increased creatinine, increased potassium, musculo-skeletal pain, chills, and pyrexia.
- Though Adstiladrin (nadofaragene firadenovec), Anktiva (nogapendekin alfa inbakicept), and Keytruda (pembrolizumab) each have different side effect profiles, there is no directly comparative evidence to establish that one therapy is better tolerated than another.

Dosing *[3]*

- Anktiva (nogapendekin alfa inbakicept) is given via intravesical administration (infused into the bladder) by a urologist and is retained in the bladder for 2 hours. It is given in combination with BCG.
- Anktiva (nogapendekin alfa inbakicept) is administered on the following schedule:

Phase	Dose	Number of doses
Induction (initial) [week 0-6]	400 mcg once per week x 6 weeks	6
Following 6 weeks [week 7-12]	No active treatment	0
At Month 3 (week 12): assess response - If complete response not achieved at 3 months (Week 12): proceed to Induction #2 [6 doses] - If complete response at 3 months (Week 12): proceed to Maintenance (initial) [15 doses]		
Induction #2(if complete response not achieved at 3 months)	400 mcg once per week x 6 weeks	6
Maintenance (initial) If complete response at 3 months (Week 12) OR after Induction #2	400 mcg once per week x 3 weeks at Month 4, 7, 10, 13, and 19	15
Maintenance (ongoing) (for complete response at Month 25 and later)	400 mcg once per week x 3 weeks at Month 25, 31, and 37	9

- A treatment course consists of 36 doses of Anktiva (nogapendekin alfa inbakicept). The safety and efficacy of repeat treatment courses has not been studied.

Appendix 1: Standard Definition of BCG Failure [7]

BCG-unresponsive CIS: Persistent or recurrent CIS alone or with recurrent Ta/T1 disease within 12 months of adequate BCG therapy.

Adequate BCG therapy is defined as at least five of six doses of an initial induction course plus at least two or three doses of maintenance BCG, or at least five of six doses of initial induction course plus at least two of six doses of a second induction course

Appendix 2: AJCC Staging of NMIBC [1] (refer to Figure 1 below)

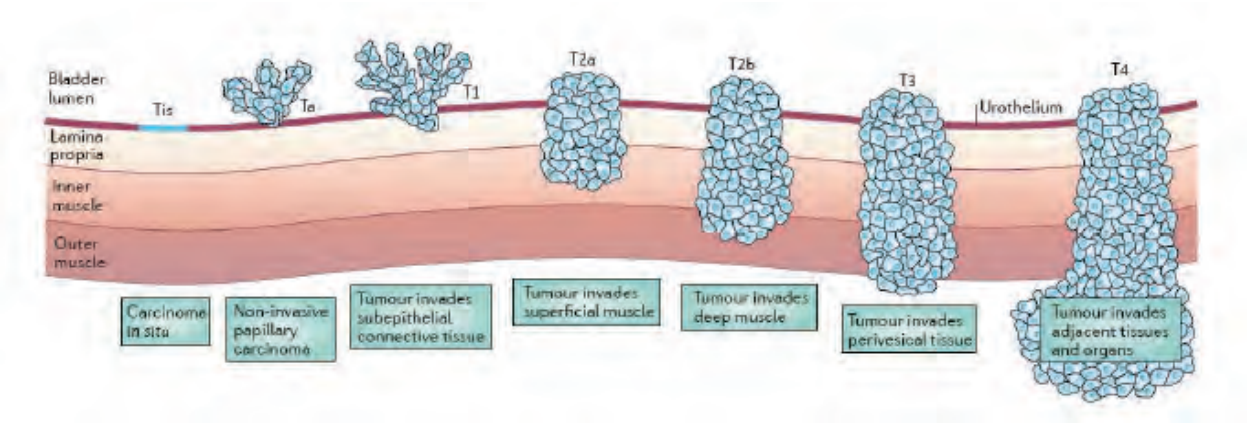
T = Primary tumor

Ta = Noninvasive papillary tumor

Tis = Urothelial carcinoma *in situ* (CIS; 'flat tumor')

T1 = Tumor invades lamina propria (subepithelial connective tissue)

Figure 1: Bladder Cancer Classification [8]



Cross References
Adstiladrin, nadofaragene firadenovec-vncg, Medication Policy Manual, Policy No. dru743
Keytruda, pembrolizumab, Medication Policy Manual, Policy No. dru367

Codes	Number	Description
HCPCS	C9169	Anktiva, nogapendekin alfa inbakicept

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Revision History

Revision Date	Revision Summary
12/12/2024	No coverage criteria changes with this annual review.
9/19/2024	New policy (effective 12/1/2024). - Policy limits coverage of Anktiva (nogapendekin alfa inbakicept) to BCG-unresponsive, high-grade NMIBC when patients are not eligible for or elect not to undergo cystectomy and are not a candidate for Keytruda (pembrolizumab) and Adstiladrin (nadofaragene firadenovec), and Anktiva (nogapendekin alfa inbakicept) will be used in combination with BCG. - All other uses are considered investigational.

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Medication Policy Manual | **Policy No:** dru792

Topic: Imdelltra, tarlatamab | **Date of Origin:** December 1, 2024

Committee Approval Date: December 12, 2024 | **Next Review Date:** 2025

Effective Date: January 15, 2025

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Imdelltra (tarlatamab) is an intravenously infused bispecific T-cell engager (BiTE) medication used in the treatment of small cell lung cancer (SCLC). It helps the immune system (T-cells) recognize and destroy cancer cells that express the DLL3 antigen. The DLL3 antigen is present in most SCLCs.

Policy/Criteria

Most contracts require pre-authorization approval of Imdelltra (tarlatamab) prior to coverage.

I. Continuation of therapy (COT): Imdelltra (tarlatamab) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Imdelltra (tarlatamab) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A, B, and C below are met:

A. A diagnosis of **extensive-stage small cell lung cancer (ES-SCLC), relapsed or refractory.**

AND

B. There was disease progression on or after platinum-based chemotherapy.

AND

C. Imdelltra (tarlatamab) will be used as monotherapy.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Imdelltra (tarlatamab) coverable only under the medical benefit (as a provider-administered medication).

B. **Initial Authorization:** When pre-authorization is approved, Imdelltra (tarlatamab) will be authorized for a step-up dose of 3 doses within the first 4 weeks, followed by up to 10 mg every two weeks, for 24 weeks, until disease progression.

C. **Continued Authorization:** When continued authorization is approved, Imdelltra (tarlatamab) will be authorized in doses up to 10 mg every two weeks, for 24 weeks, until disease progression. Authorization **shall** be reviewed at least every 24 weeks for documented benefit. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met. Specifically, documentation that the medication is providing clinical benefit, including disease stability or improvement, and lack of disease progression, based on an assessment of change in tumor burden. If there is documentation of potential disease progression, a shortened authorization (up to three months) may be approved to allow time for clarification of response to Imdelltra (tarlatamab), including clinical re-evaluation of the patient and reimaging.

PLEASE NOTE: Additional doses of Imdelltra (tarlatamab) will not be authorized without a documented recent assessment by the treating provider (such as oncologist) with objective evidence of response to therapy, such as by re-imaging and use of RECIST v1.1 (modified RECIST) criteria.

IV. Imdelltra (tarlatamab) is considered investigational when used for all other conditions.

Position Statement

Summary

- Imdelltra (tarlatamab) is an intravenously administered bispecific T-cell engager (BiTE) medication. It is indicated as a single agent for the treatment of extensive-stage small cell lung cancer (ES-SCLC) after disease progresses on or after platinum-based chemotherapy. It binds to the DLL3 antigen which is present on the majority of SCLC tumor cells.
- The intent of this policy is to allow for coverage of Imdelltra (tarlatamab) when used as a single agent therapy for ES-SCLC that has progressed after standard of care platinum-based chemotherapy.
- The accelerated approval of Imdelltra (tarlatamab) in progressive ES-SCLC is based on a preliminary open-label, single-arm, observational study that evaluated tumor response [objective response rate (ORR)] as a surrogate endpoint. There is currently no evidence that it provides any clinically meaningful benefit, and there is no comparative evidence.

- Zepzelca (lurbinectedin), and alkylating chemotherapy drug, is also approved in this treatment setting. The quality of evidence is similar to the evidence for Imdelltra (tarlatamab). There is no evidence comparing these two therapies.
- Like other BiTE therapies, Imdelltra (tarlatamab) carries a box warning for cytokine release syndrome (CRS) and neurological toxicity. Common adverse effects include neutropenia, anemia, infections, and hepatotoxicity.
- The National Comprehensive Cancer Network (NCCN) guidelines list Imdelltra (tarlatamab) among potential 'Other' recommended subsequent-line therapies for ES-SCLC.
- Imdelltra (tarlatamab) was studied and FDA approved in the doses listed in the product prescribing information. Use of doses or frequencies exceeding these quantities are considered investigational.
- The safety and effectiveness of Imdelltra (tarlatamab) have not been adequately studied in other disease settings. Therefore, use in settings other than that which is described above are considered investigational.
- *Reauthorization Criteria*: When coverage criteria are met, Imdelltra (tarlatamab) is authorized for six months (24 weeks) of therapy, after which time documentation must be provided to establish that the medication is effective. Specifically, there must be documentation of clinical benefit, including disease stability or improvement and there is a lack of disease progression, based on an assessment of change in tumor burden. Documentation of benefit must include an assessment of the most recent imaging ("restaging scans") by the treating oncologist.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Background *[1]*

- Small cell lung cancer (SCLC) makes up approximately 14% of lung cancers in the U.S. SCLC grows quickly and spreads rapidly.
- Platinum-based chemotherapy has been shown to palliate symptoms and improve overall survival; however, the majority of patients relapse after treatment, usually within the first year after diagnosis.

Clinical Efficacy

- The efficacy of Imdelltra (tarlatamab) as a single agent therapy for progressive (previously treated) extensive-stage small cell lung cancer (ES-SCLC) was evaluated in a single-arm, observational trial (n=100) [DeLLphi-304] that evaluated tumor response [objective response rate (ORR)] as a surrogate endpoint. [2, 3]
    * Patients in the study were treated with at least two prior lines of therapy. All received prior therapy with a platinum doublet (front-line standard of care).
    * Nearly all (98%) patients had metastatic disease. Twenty-three percent had brain metastasis and 39% had liver metastasis.
    * The ORR was 40% with 2% of patients having a complete response. The median duration of response was 9.7 months
    * There is no evidence comparing Imdelltra (tarlatamab) with any other therapy including Zepzelca (lurbinectedin) or best supportive care.
- Imdelltra (tarlatamab) was approved via the FDA accelerated pathway. Clinically meaningful benefit from this therapy has not been established.

Guidelines *[1]*

- The National Comprehensive Cancer Network (NCCN) small cell lung cancer guideline lists Imdelltra (tarlatamab) among 'Other' recommended regimens for the treatment of progressive ES-SCLC. Single-agent chemotherapy (e.g., topotecan, irinotecan) and Zepzelca (lurbinectedin) are also listed among potential therapies in this setting.

Reauthorization Criteria:

When coverage criteria are met, Imdelltra (tarlatamab) is authorized for six months (24 weeks) of therapy, after which time documentation must be provided to establish that the medication is effective. Specifically, there must be documentation of clinical benefit, including disease stability or improvement and there is a lack of disease progression, based on an assessment of change in tumor burden.

- The standard of care for evaluation of response to cancer therapy is use of the RECIST criteria for assessment of tumor burden,[4] as well as iRECIST criteria for some cancer immunotherapy.[5] Criteria used for assessment of response vary, depending on the tumor type and the therapy. Pivotal trials of Imdelltra (tarlatamab) BiTE therapy used the RECIST v1.1 criteria (modified RECIST) for assessment of tumor burden.[4]
- The modified RECIST, as well as iRECIST criteria, include use of quantitative and qualitative criteria for assessment of change in tumor burden for target lesions and non-target lesions. [4 6]

    * Quantitative measurements for target lesions (tumor size and % change)
    * Qualitative evaluation for non-target lesions (present/disappeared/ unequivocal progression)
- Documentation of benefit must include an assessment of the most recent imaging ("restaging scans") by the treating oncologist. Given the complexity of the evaluation, including use of the modified RECIST criteria, Imdelltra (tarlatamab) will not be reauthorized without an assessment of response to therapy, such a partial response (PR), complete response (CR), or stable disease (SD).
- Though not specific to the use of Imdelltra (tarlatamab), use of immunotherapy may result in pseudoprogression, due to immune and T-cell activation, which can appear similar to tumor flare. If there is documentation of potential disease progression ["unconfirmed progressive disease (UPD)"], a shortened authorization (up to three months) may be approved to allow time for clarification of response to Imdelltra (tarlatamab), including clinical re-evaluation of the patient and reimaging. Guidelines recommend reimaging for UPD after 4-8 weeks.
- If a patient has confirmed, unequivocal new lesions (progression of disease, PD), additional Imdelltra (tarlatamab) is not coverable. If a new lesion is equivocal, UPD reassessment by the treating oncologist with repeat imaging would apply (as noted above).

Investigational and Other Uses *[7]*

- Imdelltra (tarlatamab) is being evaluated in combination with Imfinzi (durvalumab) as a possible maintenance therapy for ES-SCLC after completion of first-line chemotherapy. However, efficacy in this setting is not established and the study is ongoing.
- Use of Imdelltra (tarlatamab) in any setting other than that/those listed under coverage criteria in Section II. is considered investigational.

Safety *[3]*

- Like other BiTE therapies, Imdelltra (tarlatamab) carries a box warning for cytokine release syndrome (CRS) and neurological toxicity. Close monitoring is required while initiating therapy.
- Use of Imdelltra (tarlatamab) is also associated with cytopenias, hepatoxicity, and hypersensitivity reactions.

Dosing *[3]*

- Imdelltra (tarlatamab) is given via intravenous infusion over 60 minutes. Step-up dosing with close monitoring is required when initiating therapy.
- The target dose (after initial step-up dosing) of Imdelltra (tarlatamab) is 10 mg every two weeks. It is administered until disease progression.

Cross References
Zepzelca, lurbinectedin, Medication Policy Manual, Policy No. dru658

Codes	Number	Description
HCPCS	J3490	Unclassified drugs

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Revision History

Revision Date	Revision Summary
12/12/2024	QL updated to include step-up dose.
9/17/2024	New policy (effective 12/1/2024). - Coverage of Imdelltra (tarlatamab) will be limited to subsequent-line treatment of extensive-stage small cell lung cancer (ES-SCLC) when used as monotherapy. - All other uses are considered investigational.

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Medication Policy Manual | **Policy No:** dru799

Topic: Rytelo, imetelstat | **Date of Origin:** March 1, 2024

Committee Approval Date: December 12, 2024 | **Next Review Date:** 2025

Effective Date: March 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

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The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Rytelo (imetelstat) is an injected medication used to reduce the need for regular red blood cell transfusions (RBCTs) in patients who have anemia associated with myelodysplastic syndromes (MDS) that has not responded to erythropoiesis stimulating agents (ESAs).

Policy/Criteria

Most contracts require pre-authorization approval of Rytelo (imetelstat) prior to coverage.

I. Continuation of therapy (COT): Rytelo (imetelstat) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Rytelo (imetelstat) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A, B, C, D, and E below are met:

A. Rytelo (imetelstat) is prescribed by, or in consultation with, a hematologist.

AND

B. A diagnosis of **myelodysplastic syndrome (MDS), low- to intermediate-1-risk**, without a del(5q) cytogenetic abnormality**.**

AND

C. Documented transfusion dependence, defined as transfusion of at least 8 units of packed red blood cells (RBCs) in the previous 16 weeks.

AND

D. Erythropoiesis-stimulating agents (ESAs) were ineffective, not tolerated, or are contraindicated.

AND

E. **When positive for ring sideroblasts (RS):** Prior therapy with Reblozyl (luspatercept) was not effective or not tolerated.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy services considers Rytelo (imetelstat) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Rytelo (imetelstat) will be authorized in doses of up to one, 7.1 mg/kg infusion every four weeks.

C. Authorization **shall** be reviewed as follows to confirm that medical necessity criteria are met, and that the medication is effective.

1. Initial authorization: Authorization shall be reviewed after 24 weeks. If there is no documented decrease in transfusion burden after 24 weeks, no further Rytelo (imetelstat) will be authorized for coverage.

NOTE: This time frame is based on response after 21 weeks (seven doses) plus time to reassess the patient.

2. Continued authorization (after the initial 24-week period): Authorization shall be reviewed annually.

3. For all authorizations (initial and continued authorization): Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit evidenced by a reduction or sustained reduction in the need for RBC transfusions (RBCTs).

IV. Rytelo (imetelstat) is considered investigational when used for MDS with a del(5q) cytogenetic abnormality and for all other conditions.

Position Statement

Summary

- Rytelo (imetelstat) is an intravenously administered medication approved for use in patients with low- to intermediate-1-risk myelodysplastic syndromes (MDS) with transfusion-dependent anemia who are no longer responding to, or are ineligible for, erythropoiesis-stimulating agents (ESAs).
- The intent of this policy is to allow coverage of Rytelo (imetelstat) when used as a single agent for MDS-associated transfusion-dependent anemia when therapy with ESAs is not effective or not an option for ring sideroblast-negative disease, and ESAs plus Reblozyl (luspatercept) is not effective or not an option for ring sideroblast-positive disease.
- The efficacy of Rytelo (imetelstat) in MDS-associated anemia is based on a small study where it was found to lead to transfusion independence at 8 and 24 weeks relative to placebo in approximately one in four patients. Reducing RBC transfusions can decrease iron overload and other risks associated with chronic RBC transfusions.
- Though it may improve anemia in some patients Rytelo (imetelstat) has not been shown to modify the course of MDS or to positively impact quality of life measures such as fatigue.
- Rytelo (imetelstat) is associated with a high incidence of grade 3 and 4 adverse effects (AEs) including neutropenia and thrombocytopenia which impact two out of every three patients who receive this therapy. This may result in the need for platelet transfusions, growth factors, and antibiotics to treat infections. These supportive measures have the potential to increase clinical burden and overall medical resource utilization.
- Reblozyl (luspatercept), another medication with a similar MDS indication, appears to have efficacy similar to Rytelo (imetelstat) but is associated with substantially fewer AEs and may be superior in patients with MDS with ring sideroblasts. A head-to-head study is necessary to better define their relative net health benefit.
- The National Comprehensive Cancer Network (NCCN) MDS guideline lists Rytelo (imetelstat) as a therapy option for patients with lower-risk MDS who have transfusion-dependent anemia that is not responsive to ESAs and Reblozyl (luspatercept).
- Rytelo (imetelstat) was studied and is FDA approved in the doses listed in the product prescribing information. Use of doses or frequencies exceeding these quantities are considered investigational.
- The safety and effectiveness of Rytelo (imetelstat) have not been adequately studied in other disease settings. Therefore, use in settings other than that which is described above are considered investigational.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit

relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.

- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Background *[1,2]*

- Myelodysplastic syndromes (MDS) are rare hematologic malignancies that are characterized by anemia, ineffective erythropoiesis, dysplastic changes in hematologic cells, and neutropenia and thrombocytopenia.
- MDS is categorized into four risk categories including low, intermediate-1, intermediate-2, and high-risk. Risk is defined using the International Prognosis Scoring System (IPSS). Patients with low- and intermediate-1 risk ('lower-risk MDS') generally have a lower risk of progression to acute myeloid leukemia (AML) and an overall better prognosis.
- Approximately 40% of lower risk MDS patients develop transfusion-dependent (TD)-anemia. Anemia-related fatigue can be severe and is among the most bothersome symptoms to patients. The need for regular transfusions also increases the clinical burden on this population and can lead to risks associated with iron overload.

Clinical Efficacy *[1,3,4]*

- The efficacy of Rytelo (imetelstat) is based on a randomized, double-blind, placebo-controlled study [IMerge] that evaluated 8-week RBC transfusion independence as the primary endpoint in patients with transfusion-dependent anemia associated with MDS.
    * The study enrolled adults with low- to intermediate-1-risk MDS. Patients had transfusion-dependent anemia defined as requiring four or more units of RBCs over an 8-week period in the 16 weeks leading up to randomization.
    * Patients were relapsed or refractory to ESAs (92%) or were ineligible for ESA therapy because they had endogenous erythropoietin levels >500 mU/mL. Six percent of the patients had prior therapy with Reblozyl (luspatercept).
    * Prior therapy with lenalidomide or hypomethylating agents was not allowed. Additionally, patients with MDS with del(5q) were excluded from enrollment.
    * Sixty-two percent of patients were positive for ring sideroblasts.
    * The rate of RBC transfusion independence was 39.8% and 15.0% at 8 weeks, and 28.0% and 3.3% at 24 weeks in the Rytelo (imetelstat) and placebo groups, respectively. The differences were statistically significant. Based on subgroup analyses, benefit extended to MDS both with and without ring sideroblasts.

Treatment effect was marginal for those with a lower transfusion burden at baseline.

- There is no data directly comparing Rytelo (imetelstat) with any other therapy used for transfusion-dependent MDS.
- Rytelo (imetelstat) has not been shown to alter the disease course or to improve survival or quality of life in patients with MDS.

Guidelines [2]

- The National Comprehensive Cancer Network (NCCN) MDS guideline recommendations for patients with lower-risk MDS with symptomatic anemia and no del(5q) cytogenetic abnormality include (Reblozyl) luspatercept, (Rytelo) imetelstat, and erythropoietin-stimulating agents (ESAs). The guideline generally recommends Reblozyl (luspatercept) prior to Rytelo (imetelstat).

Investigational and Other Uses [5]

- Rytelo (imetelstat) is being evaluated in high-risk MDS and several other conditions including myelofibrosis and solid tumors. However, these studies are ongoing and there are no published data so use in these settings is considered investigational.
- Use of Rytelo (imetelstat) in any setting other than that/those listed under coverage criteria in Section II. is considered investigational.

Safety [3]

- Use of Rytelo (imetelstat) is associated with thrombocytopenia and neutropenia which may require supportive therapies such as growth factors, antimicrobial therapy, and platelet transfusions. Infusion-related reactions are also common.
- Other adverse reactions may include elevated liver enzymes, prolonged partial thromboplastin time, arthralgias, and headache.
- Dose interruptions and reductions due to adverse effects are necessary in the majority of patients.

Dosing [3]

- Rytelo (imetelstat) is given via intravenous infusion over 2 hours at a dose of 7.1 mg/kg every 4 weeks. Premedication with antihistamines and corticosteroids is recommended prior to each infusion to decrease the risk of infusion reactions.
- Rytelo (imetelstat) should be discontinued at week 24 (after 6 doses) if treatment does not result in a decrease in RBC transfusion burden.

Cross References
Reblozyl, luspatercept-aamt, Medication Policy Manual, Policy No. dru631

Codes	**Number**	**Description**
HCPCS	J3490	Unclassified drugs

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1. Center for Drug Evaluation and Research; U.S. Food and Drug Administration Multi-Discipline Review for NDA 217-779; Rytelo™ (imetelstat). [cited 8/19/2024]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2024/217779Orig1s000MultidisciplineR.pdf.
2. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology™. [Updated routinely]. [cited with policy updates and as necessary]. Available from: https://www.nccn.org/guidelines/category_1.
3. Rytelo™ (imetelstat) [package insert]. Geron Corporation; Foster City, CA; June 2024.
4. Platzbecker U, Santini V, Fenaux P, et al. Imetelstat in patients with lower-risk myelodysplastic syndromes who have relapsed or are refractory to erythropoiesis-stimulating agents (IMerge): a multinational, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2024;403(10423):249-60. PMID: 38048786
5. National Institutes of Health, Clinicaltrials.gov [website]. [cited periodically]. Available from: www.clinicaltrials.gov.

Revision History

Revision Date	Revision Summary
12/12/2024	New policy (effective 3/1/2025). - Coverage of Rytelo (imetelstat) will be limited to patients with low- to intermediate-1-risk myelodysplastic syndrome who require at least 8 units of packed RBCs in the preceding 16 weeks when prior erythropoiesis-stimulating agents (ESAs) have not been effective for ring sideroblast-negative disease, and ESAs plus Reblozyl (luspatercept) have not been effective for ring sideroblast-positive disease. - Use in MDS with a del(5q) cytogenetic abnormality is considered investigational as well as all other uses not specifically described in the coverage criteria.

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Medication Policy Manual | **Policy No:** dru800

Topic: Tecelra, afamitresgene autoleucel | **Date of Origin:** March 1, 2024

Committee Approval Date: December 12, 2024 | **Next Review Date:** 2026

Effective Date: March 1, 2025

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Tecelra (afamitresgene autoleucel; afami-cel) is a cellular therapy that uses a patient's own genetically modified T cells to kill synovial sarcoma cells that express melanoma-associated antigen A4 (MAGE-A4).

Policy/Criteria

Most contracts require pre-authorization approval of Tecelra (afamitresgene autoleucel) prior to coverage.

I. Continuation of therapy (COT): Tecelra (afamitresgene autoleucel) may be considered medically necessary when full policy criteria below are met, including quantity limit. However, Tecelra (afamitresgene autoleucel) is not coverable for repeated doses and is not coverable if a patient has previously received prior Tecelra (afamitresgene autoleucel).

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Tecelra (afamitresgene autoleucel) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A through F below are met:

A. A diagnosis of **synovial sarcoma, unresectable locally advanced or metastatic.**

AND

B. The patient tests positive for one of the following HLA-A subtypes:

1. HLA-A*02:01P

2. HLA-A*02:02P

3. HLA-A*02:03P

4. HLA-A*02:06P

AND

C. The tumor expresses melanoma-associated antigen A4 (MAGE-A4).

AND

D. Disease progression after at least two prior systemic therapies, one of which must have included an anthracycline- or ifosfamide-based chemotherapy regimen.

AND

E. No prior gene or cellular therapy, including Tecelra (afamitresgene autoleucel).

AND

F. Patient is a suitable candidate for Tecelra (afamitresgene autoleucel) and meets all of the following criteria 1 through 3 below:

1. The patient has an ECOG performance status of 0 or 1 [or Karnofsky Performance score (KPS) of at least 80; the patient is ambulatory and able to carry out work of a light or sedentary nature].

AND

2. The patient has adequate and stable kidney, liver, and cardiac function (provider attestation).

AND

3. The patient has no active systemic infections (including, but not limited to HCV, HBV, and HIV infection) (provider attestation).

PLEASE NOTE: Suitability for Tecelra (afamitresgene autoleucel) must be documented in recent clinical documentation (such as in chart notes, laboratory reports).

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers Tecelra (afamitresgene autoleucel) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Tecelra (afamitresgene autoleucel) will be authorized in quantities of one treatment course per lifetime.

IV. Tecelra (afamitresgene autoleucel) is considered investigational for patients who are heterozygous or homozygous for HLA-A*02:05P, and when used for all other conditions.

Position Statement

Summary

- Tecelra (afamitresgene autoleucel) is an intravenously infused melanoma-associated antigen A4 (MAGE-A4)-directed genetically modified (using lentiviral vector) autologous T cell immunotherapy. It is indicated as a one-time infusion for the treatment of unresectable or metastatic synovial sarcoma in patients who have received prior chemotherapy. Patients eligible for this therapy must be HLA-A*02:01P, -A*02:02P, -A*02:03P, or -A*02:06P positive and their tumors must express MAGE-A4 antigen.
- The intent of this policy is to allow for coverage of Tecelra (afamitresgene autoleucel) for unresectable or metastatic synovial sarcoma after progression of disease on at least two prior therapies, including standard front-line chemotherapy, when patients are positive for one of the HLA subtypes listed above, their tumors express MAGE-A4, and they are found to be fit to receive this intensive therapy.
- Tecelra (afamitresgene autoleucel) received FDA accelerated approval in synovial sarcoma based on a small, single-arm, observational study that evaluated tumor response [objective response rate (ORR)] as a surrogate endpoint. There is currently no evidence that it provides any clinically meaningful benefit, and there is no comparative evidence.
- Tecelra (afamitresgene autoleucel) is associated with serious side effects including cytokine release syndrome (CRS) and neurological toxicity. Other potential side effects include gastrointestinal effects (nausea and vomiting), infections, cardiovascular effects, fatigue, and edema.
- The National Comprehensive Cancer Network (NCCN) guideline lists anthracycline- or ifosfamide-based chemotherapy as standard front-line options for unresectable or metastatic synovial sarcoma. Subsequent-line therapy may include Votrient (pazopanib), Yondelis (trabectedin), or additional chemotherapy. The guideline dose not yet include Tecelra (afamitresgene autoleucel) among these recommendations.

- Tecelra (afamitresgene autoleucel) was studied and FDA approved in the doses listed in the product prescribing information. Use of doses or frequencies exceeding these quantities are considered investigational.
- The safety and effectiveness of Tecelra (afamitresgene autoleucel) have not been adequately studied in other disease settings. Therefore, use in settings other than that which is described above are considered investigational.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Background *[1,2]*

- Synovial sarcoma is a rare type of soft tissue sarcoma (STS) making up approximately 5% of STS cases.
- Approximately 50% of synovial sarcoma cases recur or become metastatic. The overall prognosis is poor.
- It is estimated that about 67% of HLA-A*02-positive patients have MAGE-A4-expressing tumors.

Clinical Efficacy *[1,3]*

- The efficacy of Tecelra (afamitresgene autoleucel) as a therapy for locally advanced unresectable or metastatic synovial sarcoma was evaluated in a small (N=44), observational study [SPEARHEAD-1] that evaluated tumor response [objective response rate (ORR)] as a surrogate endpoint.
    * All patients were positive for HLA-A*02:01, -A*02:02, -A*02:03, -A*02:06, or other HLA-A*02 alleles with the same protein sequence as those in the peptide-biding

domain. Patients positive for HLA-A*02:05 were excluded from the study.

  * Tumors were required to have MAGE-A4 staining intensity of 2 or higher on at least 30% of tumor cells and a MAGE-A4 P score ≥30.
  * Subjects in the trial had a median of three prior therapies. All patients had prior therapy with either an anthracycline- or ifosfamide-based chemotherapy regimen.
  * Patients were required to be fit to receive Tecelra (afamitresgene autoleucel) and the intensive lymphodepleting chemotherapy required prior to its infusion. This included having good performance status, adequate organ function, and no ongoing infections.
  * The reported ORR was 43% with 2 complete responses (4.5%). The median duration of response was 6 months. Based on an FDA subgroup analysis there was no decline in response rate in patients who had received >2 prior lines of therapy versus those who had received ≤2 prior lines of therapy.
  * Tecelra (afamitresgene autoleucel) has not been compared with any other therapy.

- Tecelra (afamitresgene autoleucel) was approved via the FDA accelerated pathway. Clinically meaningful benefit from this therapy has not been established.

Guidelines *[2]*

- The National Comprehensive Cancer Network (NCCN) soft tissue sarcoma guideline lists chemotherapy (anthracycline- or ifosfamide-based regimens) as the standard front-line approach for unresectable advanced or metastatic synovial sarcoma. After progression on front-line therapies Votrient (pazopanib), Yondelis (trabectedin), and gemcitabine/ docetaxel are listed as potential options. Tecelra (afamitresgene autoleucel) is not yet part of the guideline recommendations.

Investigational and Other Uses

- Use of Tecelra (afamitresgene autoleucel) in any setting other than that/those listed under coverage criteria in Section II. is considered investigational.

Safety *[4]*

- Current safety experience is limited to the 44 patients with advanced synovial sarcoma who received a single dose of Tecelra (afamitresgene autoleucel) in the pivotal trial.
- Tecelra (afamitresgene autoleucel) labeling carries a Boxed warning describing the potential for cytokine release syndrome (CRS). Other Warnings and Precautions include immune effector cell-associated neurotoxicity syndrome (ICANS), prolonged severe cytopenia, infections, secondary malignancies and hypersensitivity reactions. Close monitoring of patients is warranted.

Dosing *[4]*

- Tecelra (afamitresgene autoleucel) is given via intravenous infusion as a single dose.
- Prior to infusion of Tecelra (afamitresgene autoleucel), four consecutive days of lymphodepleting is given.
- The safety and efficacy of repeat doses of Tecelra (afamitresgene autoleucel) has not been evaluated.

Cross References
Votrient, pazopanib, Medication Policy Manual, Policy No. dru199
Yondelis, trabectedin, Medication Policy Manual, Policy No. dru440

Codes	Number	Description
HCPCS	J3490	Unclassified drugs

References

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4. Tecelra® (afamitresgene autoleucel) [package insert]. Adaptimmune, LLC; Philadelphia, PA; August 2024.

Revision History

Revision Date	Revision Summary
12/12/2024	New policy (effective 3/1/2025). - Coverage of Tecelra (afamitresgene autoleucel) will be limited to the subsequent-line treatment (after progression on front-line chemotherapy and at least one additional therapy) of unresectable or metastatic synovial sarcoma in patients with the HLA subtypes listed in the policy when their tumors express MAGE-A4. Patients should be naïve to prior treatment with cellular therapy, including Tecelra (afamitresgene autoleucel), and must be fit to receive this intensive regimen. - Coverage is limited to one treatment course per lifetime. - Use in patients who are positive for HLA-A*02:05P is considered investigational, as is use in any other condition.

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Medication Policy Manual | **Policy No:** dru802

Topic: Niktimvo, axatilimab-csfr | **Date of Origin:** March 1, 2025

Committee Approval Date: March 6, 2025 | **Next Review Date:** 2026

Effective Date: May 1, 2025

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Niktimvo (axatilimab) is an intravenously infused colony stimulating factor-1 receptor (CSF-1R)-blocking antibody for the treatment of chronic graft-versus-host disease (cGVHD) that is refractory to standard front-line therapies.

Policy/Criteria

Most contracts require pre-authorization approval of Niktimvo (axatilimab) prior to coverage.

I. Continuation of therapy (COT): Niktimvo (axatilimab) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Niktimvo (axatilimab) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A through C below are met:

A. A diagnosis of **chronic graft-versus-host disease (cGVHD)** after allogeneic hematopoietic stem cell transplant (HSCT)**.**

AND

B. The cGVHD is refractory to corticosteroids.

AND

C. At least two additional prior systemic therapies (in addition to corticosteroids with or without calcineurin inhibitors) were not effective or not tolerated.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy services considers Niktimvo (axatilimab) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Niktimvo (axatilimab) will be authorized in doses up to 35 mg every two weeks until disease progression.

C. Authorization **may** be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

IV. Niktimvo (axatilimab) is considered investigational when used in combination with other unique cGVHD medications [e.g., Jakafi (ruxolitinib), Imbruvica (ibrutinib), Rezurock (belumosudil)], and for all other conditions.

Position Statement

Summary

- Niktimvo (axatilimab) is an intravenously administered colony stimulating factor-1 receptor (CSF-1R)-blocking antibody. It is indicated for chronic graft-versus-host disease (cGVHD) that is relapsed or refractory after at least two prior therapies.
- cGVHD occurs in 30% to 50% of patients after an allogeneic hematopoietic stem cell transplant (HSCT). It is a multisystem disorder that can lead to chronic inflammation, fibrosis, and death. The goals of treatment are to reduce symptom burden, control objective manifestations of disease activity, and to prevent damage and disability. This must all be balanced with potential toxicity related to treatments.
- The intent of this policy is to allow for coverage of Niktimvo (axatilimab) for steroid-refractory cGVHD (defined as disease progression on corticosteroids +/- calcineurin inhibitors) when at least two prior therapies have been ineffective or are not tolerated.
- The approval of Niktimvo (axatilimab) is based on a small, single-arm, observational study that reported a disease response rate of 75% after six months of treatment. There were no complete responses. Additional evidence is needed to determine if Niktimvo (axatilimab) improves or preserves organ function, improves disease symptoms, or prevents disability.
- Niktimvo (axatilimab) has not been compared with any other cGVHD therapy including Imbruvica (ibrutinib), Jakafi (ruxolitinib), and Rezurock (belumosudil) which are also FDA-approved for use in relapsed or refractory cGVHD.
- Like other antibody therapies, Niktimvo (axatilimab) carries a warning for infusion-related reactions. Common adverse effects include infections, gastrointestinal symptoms, fatigue, musculoskeletal pain, and dyspnea.
- The National Comprehensive Cancer Network (NCCN) guideline lists Niktimvo (axatilimab) among recommendations for steroid-refractory cGVHD after two or more prior lines of therapy.

- Niktimvo (axatilimab) was studied and is FDA approved in the doses listed in the product prescribing information. Use of doses or frequencies exceeding these quantities are considered investigational.
- The safety and effectiveness of Niktimvo (axatilimab) have not been adequately studied in other disease settings. Therefore, use in settings other than that which is described above are considered investigational.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Background *[1,2]*

- Chronic graft-versus-host disease (cGVHD) occurs in 30% to 50% of patients after an allogeneic hematopoietic stem cell transplant (HSCT). It is a multisystem disorder that can lead to chronic inflammation, fibrosis, and death.
- Per the National Institutes of Health (NIH) consensus criteria, systemic therapy is indicated for patients with involvement of three or more organs, moderate- to severe involvement in any organ, or any lung involvement.
- The goals of treatment are to reduce symptom burden, control objective manifestations of disease activity, and to prevent damage and disability. This must all be balanced with potential toxicity related to treatments.

Clinical Efficacy *[3,4]*

- The efficacy of Niktimvo (axatilimab) for the management of relapsed or refractory cGVHD is based on a small (N=79), single-arm, observational study [AGAVE-201] that reported a partial response rate of 75% after six months of treatment.

    * Patients enrolled in the study had a diagnosis of steroid-refractory relapsed or refractory cGVHD after an allogeneic HSCT. Fifty-seven percent of patients had involvement of four or more organs and 80% had disease considered to be severe.
    * Patients were allowed to continue their standard of care systemic cGVHD therapies (e.g., corticosteroids, calcineurin inhibitors) if they were on a stable dose for at least two weeks prior to entering the study.
    * Disease was no longer responsive to at least two prior therapies (median of four with a range of 2 to 12). Forty-seven percent were refractory to their last therapy.
    * Prior therapies included: Corticosteroids (100%), ibrutinib (34%), ruxolitinib (72%), belumosudil (20%).
    * A partial response was demonstrated in 75% of the patients in the study. There were no complete responses reported.
- Additional evidence is needed to determine if it improves or preserves organ function, improves disease symptoms, or prevents disability.
- There is no evidence directly comparing any of the FDA-approved agents for recurrent or refractory cGVHD which includes Niktimvo (axatilimab), Imbruvica (ibrutinib), Jakafi (ruxolitinib), and Rezurock (belumosudil).
- Jakafi (ruxolitinib) has the best evidence among these agents where it was shown to demonstrate higher response rates than best available therapy (e.g., steroids and calcineurin inhibitors) in a steroid-refractory population with cGVHD. The evidence for Imbruvica (ibrutinib) and Rezurock (belumosudil) is of similar type and quality (small, single-arm studies) as Niktimvo (axatilimab).

Guidelines [2]

- The National Comprehensive Cancer Network (NCCN) hematopoietic cell transplantation guideline lists the following recommendations for the management of cGVHD:
    * *Steroid-refractory cGVHD:* Jakafi (ruxolitinib) [category 1]
    * *After one or more prior lines of therapy:* Imbruvica (ibrutinib) [category 2A]
    * *After two or more prior lines of therapy:* Rezurock (belumosudil), and Niktimvo (axatilimab) [category 2A]

Investigational and Other Uses [4]

- The use of Niktimvo (axatilimab) in combination with other unique cGVHD medications [e.g., Jakafi (ruxolitinib), Imbruvica (ibrutinib), and Rezurock (belumosudil)] has not been studied and is considered investigational.
- Use of Niktimvo (axatilimab) in any setting other than what is listed under coverage criteria in Section II. is considered investigational.

Safety [3]

- Grade 3 and 4 adverse reactions reported in the pivotal trial include infections, gastrointestinal effects, fatigue, and dyspnea.
- Package labeling warns of the potential for infusion-related reactions.

Dosing *[3]*

- Niktimvo (axatilimab) is administered intravenously every two weeks at a dose of 0.3 mg/kg (maximum of 35 mg) and is given until disease progression.
- Niktimvo (axatilimab) is indicated for adult and pediatric patients with a weight >40 kg.

Cross References
Bruton's tyrosine kinase (BTK) inhibitors, Medication Policy Manual, Policy No. dru691 *[includes Imbruvica (ibrutinib)]*
Jakafi, ruxolitinib, Medication Policy Manual, Policy No. dru268
Rezurock, belumosudil, Medication Policy Manual, Policy No. dru684

Codes	**Number**	**Description**
HCPCS	J3490	Unclassified drugs

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3. Niktimvo™ (axatilimab) [package insert]. Incyte Corporation; Wilmington, DE; August 2024.
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Revision History

Revision Date	**Revision Summary**
3/6/2025	No changes to coverage criteria with this annual review.
12/12/2024	New policy (effective 3/1/2025). - Coverage of Niktimvo (axatilimab) will be limited to patients with steroid-refractory (i.e., disease progression on corticosteroids with or without calcineurin inhibitors) cGVHD after at least two additional lines of therapy. - All other uses are considered investigational.

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Medication Policy Manual | **Policy No:** dru803

Topic: Vyloy, zolbetuximab | **Date of Origin:** May 1, 2025

Committee Approval Date: March 6, 2025 | **Next Review Date:** 2025

Effective Date: May 1, 2025

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Vyloy (zolbetuximab) is an intravenously administered claudin 18.2 (CLDN18.2)-directed cytolytic antibody used in the treatment of specific types of cancer [advanced gastric or gastroesophageal junction cancer (GEJ)].

Policy/Criteria

Most contracts require pre-authorization approval of Vyloy (zolbetuximab) prior to coverage.

I. Continuation of therapy (COT):

Vyloy (zolbetuximab) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND there is documentation that the medication was covered by another health plan. Examples of documentation include the coverage approval letter from the previous health plan or paid claim.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients):

Vyloy (zolbetuximab) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A through E below are met:

A. A diagnosis of **gastric or gastroesophageal junction (GEJ) adenocarcinoma, locally advanced unresectable or metastatic.**

AND

B. The tumor is human epidermal growth factor receptor 2 (HER2)-negative.

AND

C. The tumor is claudin (CLDN) 18.2-positive, defined as ≥75% of tumor cells demonstrating moderate to strong membranous CLDN18 staining determined by immunohistochemistry (IHC).

AND

D. There has been no prior systemic therapy in the locally advanced unresectable or metastatic setting.

AND

E. Vyloy (zolbetuximab) will be used in combination with fluoropyrimidine (e.g. fluorouracil or capecitabine)- plus platinum (e.g. cisplatin or oxaliplatin)-containing chemotherapy.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy services considers Vyloy (zolbetuximab) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Vyloy (zolbetuximab) will be authorized in the following doses until disease progression:

1. **Initial dose:** 800 mg/m^2 once.
2. **Subsequent doses:** 600 mg/m^2 every 3 weeks, or 400 mg/m^2 every 2 weeks.

C. Reauthorization: Authorization **shall** be reviewed at least every 24 weeks for documented benefit. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met. Specifically, documentation that the medication is providing clinical benefit, including disease stability or improvement, and lack of disease progression, based on an assessment of change in tumor burden. If there is documentation of potential disease progression, a shortened authorization (up to three months) may be approved to allow time for clarification of response to Vyloy (zolbetuximab), including clinical re-evaluation of the patient and reimaging.

PLEASE NOTE: Additional doses of Vyloy (zolbetuximab) will not be authorized without a documented recent assessment by the treating provider (such as oncologist) with objective evidence of response to therapy, such as by re-imaging and use of the RECIST 1.1 and/or iRECIST criteria.

IV. Investigational Uses:

Vyloy (zolbetuximab) is considered investigational when used in combination with programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor medications, other anticancer monoclonal antibodies [such as Cyramza (ramucirumab) or Erbitux (cetuximab)], and for all other conditions not addressed in the coverage criteria above.

Position Statement

Summary

- Vyloy (zolbetuximab) is an intravenously administered claudin 18.2 (CLDN18.2)-directed cytolytic antibody. It is indicated in combination with fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of human epidermal growth factor receptor 2 (HER2)-negative, unresectable (locally advanced) or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma when tumors are CLDN18.2-positive.
- *CLDN18.2 testing*: is required for coverage There is currently no FDA-approved companion diagnostic for evaluating tumor CLDN18.2 expression. The current standard for determining CLDN18.2-postive tumors, and that which was used in the pivotal trial evaluating Vyloy (zolbetuximab), is defined as ≥75% of tumor cells demonstrating moderate to strong (2+ or 3+) membranous CLDN18.2 immunohistochemical staining.
- The intent of this policy is to allow coverage of Vyloy (zolbetuximab) when used in the population for which it is indicated as described above.
- The approval of Vyloy (zolbetuximab) in CLDN18.2-positive, HER2-negative, unresectable locally advanced or metastatic gastric or GEJ adenocarcinoma is based on one trial where it demonstrated a significant improvement in median overall survival (OS) when used in combination with fluoropyrimidine- and platinum-containing chemotherapy relative to chemotherapy alone.
- Use in subsequent-line settings or in combination with programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitors or other anti-cancer monoclonal antibodies is considered investigational as Vyloy (zolbetuximab) has not been formally evaluated in these settings.
- Vyloy (zolbetuximab) is associated with significant adverse (AEs) effects which may impact its tolerability. These AEs include nausea and vomiting, other gastrointestinal effects, fatigue, and hypersensitivity reactions. AEs leading to dose interruption were greater in the Vyloy (zolbetuximab) plus chemotherapy arm than in the chemotherapy alone arm (75% versus 40%, respectively).
- The National Comprehensive Cancer Network (NCCN) gastric cancer guideline lists Vyloy (zolbetuximab) in combination with a fluoropyrimidine plus oxaliplatin as a treatment option for CLDN18.2-positive, HER2-negative, unresectable locally advanced or metastatic gastric or GEJ adenocarcinoma.
- Vyloy (zolbetuximab) was studied and FDA approved in the doses listed in the product prescribing information. It is administered until disease progression or unacceptable toxicity. Use of doses or frequencies exceeding these quantities is considered investigational.
- The safety and effectiveness of Vyloy (zolbetuximab) have not been adequately studied in other disease settings. Therefore, use in settings other than that which is described above is considered investigational.
- *Reauthorization Criteria*: When coverage criteria are met, Vyloy (zolbetuximab) is authorized for up to six months (up to 24 weeks) of therapy, after which time documentation must be provided to establish that the medication is effective. Specifically,

there must be documentation of clinical benefit, including disease stability or improvement and there is a lack of disease progression, based on an assessment of change in tumor burden. Documentation of benefit must include an assessment of the most recent imaging ("restaging scans") and/or re-biopsy by the treating oncologist.

Regence Pharmacy Services performs independent analyses of oncology medication evidence, to establish coverability per the contracts with the health plan.

- Most contracts define coverability based on established clinical benefit in published, peer-reviewed literature, along with consideration of regulatory status.
- FDA approval does not in itself establish medical necessity, as unpublished, low-quality evidence, including exploratory analyses and unvalidated surrogate endpoints, may be used as the basis of approval. Regulatory approval may or may not reflect clinical benefit relative to standard of care and the recommendations of expert clinical advisors such as the Oncologic Drugs Advisory Committee (ODAC). FDA approvals generally do not consider cost compared to established therapies, or value to members.
- Likewise, NCCN clinical practice guidelines assignment of a recommendation (category 1, 2a, or 2b) does not necessarily establish medically necessity. NCCN recommendations are inconsistently supported by published, peer-reviewed literature and do not uniformly consider value of new therapies relative to existing potentially higher-value treatment options, considering effectiveness, safety, and cost.
- Medication coverage criteria are developed based on the 'medical necessity' assessment, as described above.

Regence Pharmacy Services analysis and coverage policy may differ from FDA labeled indication and/or NCCN clinical practice guidelines.

Background [1]

- Over 95% of gastric cancers are adenocarcinomas. Gastric cancer tends to have a poor prognosis in Western countries where it is less common because it is more often diagnosed in advanced stages.
- Selecting a therapy for gastric or GEJ cancer involves screening for several different biomarkers. This includes determining human epidermal growth factor receptor 2 (HER2) status, microsatellite instability (MSI) status, programmed death-ligand 1 (PD-L1) expression, neurotrophic tropomyosin-related kinase (NTRK) gene fusion status, and claudin (CLDN) 18.2 expression.
    * Approximately 15% of gastric cancers are HER2-positive.
    * Between 27% to 52% of gastric cancers are estimated to be CLDN18.2-postive.
    * Some tumors may be positive for both PD-L1 and CLDN18.2; however, the proportion of tumors with this characteristic is not yet known.

Clinical Efficacy [2 3]

- The efficacy of Vyloy (zolbetuximab) as an add on to a fluoropyrimidine plus oxaliplatin chemotherapy (FOLFOX6 regimen) for advanced, HER2-negative, CLDN18.2-positive

gastric or gastroesophageal junction (GEJ) cancer is based on a randomized, double-blind trial [SPOTLIGHT] that demonstrated an overall survival (OS) advantage relative to chemotherapy alone (placebo group).

* The trial enrolled adults with HER2-negative unresectable locally advanced or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma. About 30% of the population had a previous gastrectomy.
* The tumors were required to be CLDN18.2-positive which was defined as ≥75% of tumor cells with moderate- to strong (2+ or 3+) membranous CLDN18.2 staining (There is no FDA-approved companion diagnostic to date).
* Patients had no prior systemic therapy for advanced disease; however, neoadjuvant or adjuvant chemotherapy or immunotherapy was allowed if it was completed at least six months prior to randomization.
* The median OS was 18.2 months and 15.5 months in the Vyloy (zolbetuximab) and placebo arms, respectively (HR 0.75 [95% CI: 0.60, 0.94]; p=0.0053).

- Only 10% of the study population was enrolled in the U.S. which may impact generalizability due to varying treatment standards and disease characteristics across populations.

Reauthorization Criteria

- When coverage criteria are met, Vyloy (zolbetuximab) is authorized for six months (24 weeks) of therapy, after which time documentation must be provided to establish that the medication is effective. Specifically, there must be documentation of clinical benefit, including disease stability or improvement and there is a lack of disease progression, based on an assessment of change in tumor burden.
  * The standard of care for evaluation of response to immunotherapy, including anticancer monoclonal antibody therapies such as Vyloy (zolbetuximab), is use of the iRECIST criteria for assessment of tumor burden.[4]
  * The iRECIST criteria include use of quantitative and qualitative criteria for assessment of change in tumor burden for target lesions and non-target lesions. [5]
    - Quantitative measurements for target lesions (tumor size and % change)
    - Qualitative evaluation for non-target lesions (present/disappeared/ unequivocal progression)
  * The pivotal trial for Vyloy (zolbetuximab) used the RECIST 1.1 criteria [6] for assessment of tumor burden, a standardized framework for tumor response to therapy. However, RECIST 1.1 was designed for response to cytotoxic chemotherapy and may not accurately reflect response to immunotherapy, such as Vyloy (zolbetuximab), given the cytolytic mechanism as well as antibody properties. Therefore, both the RECIST 1.1 and iRECIST criteria are used for guidance of reauthorization review for response to immunotherapy, including anticancer monoclonal antibody therapies such as Vyloy (zolbetuximab).
  * Documentation of benefit must include an assessment of the most recent imaging ("restaging scans") by the treating oncologist. Given the complexity of the evaluation, including use of the RECIST 1.1 and/or iRECIST criteria, anticancer

monoclonal antibody therapies, such as Vyloy (zolbetuximab), will not be reauthorized without an assessment of response to therapy, such a partial response (PR), complete response (CR), or stable disease (iSD).

* Use of some immunotherapies may result in pseudoprogression, due to immune and T-cell activation, which can appear similar to tumor flare. If there is documentation of potential disease progression ["unconfirmed progressive disease (iUPD)"], a shortened authorization (up to three months) may be approved to allow time for clarification of response to immunotherapy, including clinical re-evaluation of the patient and reimaging. Guidelines recommend reimaging for iUPD after 4-8 weeks.
* If a patient has confirmed, unequivocal new lesions (progression of disease, iPD), additional doses of immunotherapy, including anticancer monoclonal antibody therapies such as Vyloy (zolbetuximab), is not coverable. If a new lesion is equivocal, iUPD reassessment by the treating oncologist with repeat imaging would apply (as noted above).

Guidelines [1]

- The National Comprehensive Cancer Network (NCCN) gastric cancer guideline lists Vyloy (zolbetuximab) plus a fluoropyrimidine and oxaliplatin as a preferred treatment option for HER2-negative, CLDN18.2-positive, unresectable locally advanced or metastatic gastric or GEJ cancer.

Investigational and Other Uses [7]

- *Pancreatic cancer*: There is interest in combining Vyloy (zolbetuximab) in CLDN18.2-positive pancreatic cancer. However, there is currently no published data supporting use in this setting.
- *Combination therapy:*
  * Programmed death receptor-1 (PD-1) inhibitors are used to treat HER2-negative gastric and GEJ tumors that express programmed death-ligand 1 (PD-L1); however, use of Vyloy (zolbetuximab) in combination with these therapies has not been studied to date. The pivotal Vyloy (zolbetuximab) study did not allow concomitant use of PD-1 inhibitors.
  * In addition, there is no published data supporting use in combination with other anticancer monoclonal antibodies, such as Cyramza (ramucirumab) or Erbitux (cetuximab).
- Use of Vyloy (zolbetuximab) in any disease setting other than those listed under coverage criteria above is considered investigational.

Safety [2 8]

- Hypersensitivity reactions and severe nausea and vomiting are among the Warnings and Precautions listed for Vyloy (zolbetuximab).
- The most common adverse effects (AEs) associated with use of Vyloy (zolbetuximab) include gastrointestinal effects (e.g., nausea, vomiting, diarrhea), fatigue, peripheral sensory neuropathy, hypersensitivity, and pyrexia.

- AEs leading to dose interruption were greater in the Vyloy (zolbetuximab) plus chemotherapy arm than in the chemotherapy alone arm (75% versus 40%, respectively)

Dosing *[8]*

- Vyloy (zolbetuximab) is administered intravenously in combination with fluoropyrimidine- and platinum-containing chemotherapy in the following doses:
  * **Initial dose:** 800 mg/m^2 once.
  * **Subsequent doses:** 600 mg/m^2 every 3 weeks or 400 mg/m^2 every 2 weeks.
- Premedication with a combination of antiemetics is required prior to each infusion.

Cross References
PD-1 and PD-L1 Inhibitor Monoclonal Antibody Therapies, Medication Policy Manual, Policy No. dru797

Codes	**Number**	**Description**
HCPCS	J3490	Unclassified drug

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Revision History

Revision Date	Revision Summary
3/6/2025	New policy (effective 5/1/2025). - Coverage of Vyloy (zolbetuximab) will be limited to patients with CLDN18.2-positive, human epidermal growth factor receptor 2 (HER2)-negative, unresectable (locally advanced) or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma when used in combination with fluoropyrimidine- and platinum-containing chemotherapy as a first-line therapy. - All other uses are considered investigational.

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Medication Policy Manual

Policy No: dru806

Topic: Non-Factor Hemophilia A and B Prophylactic Products

- Alhemo, concizumab-mtci
- Hympavzi, marstacimab-hncq

Date of Origin: April 15, 2025

Committee Approval Date: March 6, 2025

Next Review Date: 2025

Effective Date: April 15, 2025

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Non-factor hemophilia A and B prophylactic products are used for routine prophylaxis to prevent or decrease the frequency of bleeding episodes in patients with either hemophilia A or B.

Policy/Criteria

Most contracts require pre-authorization approval of non-factor hemophilia A and B prophylactic products (including all drugs as listed in *Table 1*) prior to coverage.

I. Continuation of therapy (COT):

Non-factor hemophilia A and B prophylactic products may be considered medically necessary for COT when criterion A **AND** B below are met.

A. One of the following (1, 2 or 3):

1. For diagnoses NOT listed in the coverage criteria below, full policy criteria must be met for coverage.

OR

2. For diagnoses listed in the coverage criteria below, criteria a through d must be met:

a. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

b. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

NOTE: Please include baseline annualize bleeding rate (prior to use of non-factor hemophilia A and B prophylactic products), as well as current symptoms, for establishing documentation of clinical benefit.

OR

3. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

AND

B. "Administration, Quantity Limitations, and Authorization Period" below applies, as well as "Not Medically Necessary" for combination therapy and "Investigational Uses."
NOTE: For doses above those listed in Initial Quantities, documentation of need for higher dosing must be met, as detailed in the table.

Please note: *Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients):

Non-factor hemophilia A and B prophylactic products may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) confirming that criterion A or B below are met.

A. Hemophilia A or B with inhibitors (also referred to 'high titer factor inhibitors"), when criteria 1, 2, and 3 below are met:

1. Drug: Request is for Alhemo (concizumab).

2. Diagnosis: Both criteria a. AND b. below are met:

a. One of the following diagnoses, established by or in consultation with a hematologist (a. or b.):

i. Hemophilia A (congenital FVIII deficiency)

OR

ii. Hemophilia B (congenital FIX deficiency)

AND

b. High titer factor inhibitors: Documentation of a history of high anti-FVIII or anti-FIX titer (≥6 Bethesda units).

3. Step therapy: For hemophilia A only: Hemlibra (emicizumab) has been ineffective, not tolerated, or is medically contraindicated.

OR

B. Hemophilia A or B without inhibitors (also referred to "with low or no titer factor inhibitors"), when criteria 1, 2, and 3 below are met:

1. Drug: Request is for Hympavzi (marstacimab):

2. Diagnosis One of the following diagnoses, established by or in consultation with a hematologist (a. or b.):

a. Severe hemophilia A (congenital FVIII deficiency; FVIII activity <1)

OR

b. Moderate to severe hemophilia B (congenital FIX deficiency; FIX activity ≤2).

3. Step therapy: Both criteria a. AND b. below are met:

a. For all patients: Factor replacement product therapy is not a sufficient treatment option, defined as ONE of the following (i. or ii.):

i. Use is medically contraindicated: there is a documented objective clinical reason (as listed in *Appendix 1*) that all available extended half-life (EHL) factor products are not appropriate (as listed in *Appendix 2 and 3*).

OR

ii. Use is ineffective: Prophylactically administered EHL factor product(s) (as listed in *Appendices 2 & 3*) have been

ineffective, as defined by the patient continuing to have documented clinically significant bleeding events despite adherence to optimized EHL factor products (dose and dose frequency, as listed in *Appendices 2 and 3*), such as target joint bleeds or other end-organ damage, documented in a bleed diary or detailed provider notes.

PLEASE NOTE: On-demand ("PRN") use of a factor products (short half-life or extended half-life) will not meet the intent of this efficacy criteria.

AND

b. For hemophilia A only: Hemlibra (emicizumab) has been ineffective, not tolerated, or is medically contraindicated.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers non-factor hemophilia A and B prophylactic products coverable under the medical benefit or pharmacy benefit. Determination of coverage under the pharmacy or medical benefit is based on group-specific benefits, as defined in the group and member contract (as determined by the member contract with the health plan, regardless of self- or provider-administration).

B. When pre-authorization is approved, non-factor hemophilia A and B prophylactic products will be authorized in quantities as follows in *Table 1* below:

TABLE 1. Non-factor Hemophilia A and B Prophylactic Products

Product	Quantity Limit
Alhemo (concizumab)	Initial: up to 1 mg/kg once (loading dose) followed by 0.2 mg/kg daily for up to 1 month, then up to 0.25 mg/kg daily for 5- months (6-months total for initial authorization) Maintenance: up to 0.25 mg/kg daily for 12-months.
Hympavzi (marstacimab)	Initial: up to **53** (150 mg) **pens** in a **12- month period**, based on a one-time 300 mg loading dose followed by weekly 150 mg SC injections. Maintenance: up to **52** (150 mg) **pens** in **a 12- month period**, based on once weekly 150 mg SC injections. Dose escalation: For patients ≥50 kg, up to **104** (150 mg) **pens** in a **12-month period,** based on once weekly 300 mg SC injections, may may be considered medically necessary when there is clinical documentation that current treatment with Hympavzi 150 mg weekly has had an inadequate response (defined as two or more breakthrough bleeds requiring treatment) after at least a 6-month treatment course.

C. Doses authorized will be based on the closest available pen size.

D. Doses greater than listed above (Table 1) are considered investigational.

E. **Continued Authorization:** Authorization **shall** be reviewed at least annually to confirm that the medication continues to be effective. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as improvement in annualized bleed rate (ABR).

IV. Not Medically Necessary Uses

Non-factor hemophilia A and B prophylactic product are considered not medically necessary when used in combination with prophylactic extended half-life (EHL) FVIII or FIX products (such as those *Appendix 2 & 3*).

V. Investigational Uses

Non-factor hemophilia A and B prophylactic products are considered investigational when used for all other conditions, including but not limited to:

A. Use in combination with other non-factor hemophilia A or B prophylactic products, including but not limited to products listed in Table 1 or Hemlibra (emicizumab).

Position Statement

Summary

- Non-factor hemophilia A and B prophylactic products (as listed in Table 1) are indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients with hemophilia A (congenital factor VIII deficiency) or hemophilia B (congenital factor IX deficiency).
- The intent of this policy is to allow for coverage of non-factor hemophilia A and B prophylactic products for up to FDA-approved doses for patients with moderate to severe disease and standard of care is not effective, not tolerated, or not a treatment option.
- *Hemophilia A or B with inhibitors*:
    * Alhemo (concizumab) was studied in a phase 3 trial in patients with hemophilia A or B *with* inhibitors (defined as six or more Bethesda units), where it was shown to reduce bleeding when used in doses up to the coverable amount.
    * For patients with hemophilia A only, step with Hemlibra (emicizumab): There is no head-to-head evidence that non-factor hemophilia A and B prophylactic products prophylaxis (such as Alhemo) are safer or more effective than prophylactic Hemlibra (emicizumab), but they are more costly. Therefore, non-factor hemophilia A and B prophylactic products are coverable only when Hemlibra (emicizumab) is ineffective, or use is medically contraindicated.
- *Hemophilia A or B without inhibitors*:
    * Hympavzi (marstacimab) was studied in a phase 3 trial in patients with severe hemophilia A or moderate to severe hemophilia B as defined in coverage criteria, in patients without inhibitors. Patients on Hympavzi (marstacimab) had less

bleeds than “on-demand” factor product dosing; Hympavzi (marstacimab) was non-inferior to factor routine prophylaxis.

* In patients without inhibitors, there is no head-to-head evidence that non-factor hemophilia A and B prophylactic products prophylaxis are safer or more effective than prophylactic factor replacement regimens (FVIII or FIX) or Hemlibra (emicizumab; for hemophilia A only), but they are more costly. Therefore, non-factor hemophilia A and B prophylactic products are coverable only when EHL factor replacement products and Hemlibra (emicizumab; for hemophilia A only) are ineffective, or all are medically contraindicated.

- The National Hemophilia Foundation's Medical and Scientific Advisory Council (MASAC) recommends that bleeding prophylaxis be the standard treatment approach for individuals with severe hemophilia A or B.
    * Hemophilia A or B **without** inhibitors: Patients with hemophilia A without inhibitors typically receive prophylaxis with factor VIII replacement products or Hemlibra (emicizumab). Patients with hemophilia B without inhibitors typically receive prophylaxis with factor IX replacement products. There are numerous treatment options in this population and no distinction is made between different factor products.
    * Hemophilia A **with** inhibitors: MASAC consider Hemlibra (emicizumab) first-line for patients with hemophilia A with inhibitors. The World Federation of Hemophilia (WFH) recommends Hemlibra (emicizumab) prophylaxis over bypassing agents for patients with hemophilia A and persistent inhibitors.
- Non-factor hemophilia A and B prophylactic products may be covered for up to doses/intervals stated in the coverage criteria; the dose studied in clinical trials. The safety and effectiveness of higher doses have not been established.
- The safety and effectiveness of non-factor hemophilia A and B prophylactic products in conditions other than listed in the coverage criteria have not been established.
- *Combination use*:
    * Non-factor hemophilia A and B prophylactic products are used for “baseline” prophylaxis of bleeding and may be used in combination with on-demand (PRN) short half-life (SHL) factor products in patients without high-titer factor inhibitors. However, the use of non-factor hemophilia A and B prophylactic products (as listed in Table 1) in combination with prophylactic extended half-life (EHL) factor product (as listed in Appendix 2 & 3) is considered “not medically necessary.” There is no evidence to support the use of EHL factor products as safer or more effective than lower-cost SHL factor products when used in combination with non-factor hemophilia A and B prophylactic products.
    * There is no data for use of non-factor hemophilia A and B prophylactic products (as listed in Table 1) in combination with Hemlibra (emicizumab), another non-factor prophylactic product for hemophilia A. Therefore, use in combination with Hemlibra (emicizumab) is investigational.

- *Other Investigational Uses*: The safety and efficacy of non-factor hemophilia A and B prophylactic products (as listed in Table 1) in conditions other than Hemophilia A or B with inhibitors (as detailed in the coverage criteria), or use combination with one another or with other non-factor prophylactic therapies, including but not limited to Hemlibra (emicizumab) have not been established.

Clinical Efficacy

Hemophilia A or B **with** inhibitors

- The evidence for efficacy for Alhemo (concizumab) was based primarily on the open-label, phase III Explorer-7 trial, in which 52 patients with hemophilia A and B with inhibitors continued an on-demand bypassing agent or received Alhemo (concizumab).[1 2]
    * Patients enrolled in the trial had congenital hemophilia A or B (any severity)
    * All patients had a history of high anti-factor titers (also known as inhibitors, defined as 0.6 or higher Bethesda units).
    * Patients initially received concizumab at 1 mg/kg on Day 1, followed by a daily dose of 0.25 mg/kg starting on Day 2. However, due to thromboembolic events, the study was paused in March 2020. When the study resumed in August 2020, the dosing regimen was modified to:
        - 1 mg/kg loading dose on Day 1
        - 0.2 mg/kg daily maintenance dose starting on Day 2
    * Patients' plasma concizumab concentrations were measured at Week 4, and the dose was adjusted as follows:
        - Patients with concentrations between 200-4000 ng/mL remained on the 0.2 mg/kg daily dose
        - Patients with concentrations <200 ng/mL were increased to 0.25 mg/kg daily
        - Patients with concentrations >4000 ng/mL were decreased to 0.15 mg/kg daily
    * The annualized bleed rate (ABR) of treated bleeds was 1.7 with Alhemo (concizumab) compared to 11.8 with on-demand bypassing agent therapy (86% reduction; P<0.001); 64% of patients on Alhemo (concizumab) had no bleeds.
    * The pivotal trial for Alhemo (concizumab) was temporarily paused due to nonfatal thromboembolic events but was resumed after implementation of risk-mitigation measures including individualized dosing based on concizumab plasma concentrations. No thromboembolic events were reported after Alhemo (concizumab) was restarted.

Hemophilia A or B **without** inhibitors

- The pivotal trial for efficacy of Hympavzi (marstacimab) was the open-label, phase III BASIS trial (n=116) in which patients with severe hemophilia A or moderate to severe hemophilia B without inhibitors were observed for 24-weeks (while continuing factor products) then given Hympavzi (marstacimab) for 32 weeks.[3-5]

    * Patients in this trial had either severe hemophilia A (defined as factor VIII <1%) or moderately severe to severe hemophilia B (defined as FIX <2%).
    * Patients did not have inhibitors (also known as high anti-factor titers).
    * Patients on Hympavzi (marstacimab) experienced a 92% reduction in annualized bleeding rate (ABR) of treated bleeds compared to on-demand treatment with factor products (superiority; ABR 3.2 vs 38, respectively) and a 35% reduction in ABR of treated bleeds compared to routine prophylaxis with factor products (non-inferiority; ABR 5.1 vs 7.9, respectively). However, the ABR for routine prophylaxis with factor products was higher than expected based on results from other trials and may be due to inadequate optimization in baseline therapy; therefore, it is not possible to make a valid comparison to optimized prophylactic factor therapy.
    * A year-long, open-label trial demonstrated that patients maintained a mean annualized bleeding rate (ABR) consistent with the results seen at 32 weeks.[6]
- Non-factor hemophilia A and B prophylactic products are used for "baseline" prophylaxis of bleeding and may be used in combination with on-demand (PRN) short half-life (SHL) factor products in patients without high-titer factor inhibitors. However, the use of non-factor hemophilia A and B prophylactic products (as listed in Table 1) in combination with prophylactic extended half-life (EHL) factor product (as listed in Appendix 2 & 3) is considered "not medically necessary." There is no evidence to support the use of EHL factor products as safer or more effective than lower-cost SHL factor products when used in combination with non-factor hemophilia A and B prophylactic products.

Clinical Guidelines/Standard of Care Treatment [7-10]

- Prophylaxis is recommended as the optimal treatment modality for individuals with severe hemophilia by the National Hemophilia Foundation's Medical and Scientific Advisory Council (MASAC). The concept was conceived from the observation that moderate hemophiliacs (clotting factor level >1 IU/dL) seldom experience spontaneous bleeding and have much better preservation of joint function. Goals of therapy include trough factor levels of at least 1% (>3%-5% or higher if feasible) and minimal to no spontaneous bleeding.
- Clinical practice guidelines from MASAC consider use of factor replacement products to be the standard of care for the treatment of hemophilia A or B without inhibitors. Hemlibra (emicizumab) is also recommended as first-line in patients with severe hemophilia A with or without inhibitors.
- Factor concentrate products (factor replacement products) are effective for the prevention and control of bleeding versus no treatment based on years of significant clinical experience, systematic reviews, and are endorsed by clinical practice guidelines. There is insufficient evidence that any factor replacement products (also known as "factor concentrate") or bypassing agent is superior to another due to a lack of comparative trial data.

* There are numerous factor replacement products available for hemophilia A or B in patients without inhibitors.
* For patients with inhibitors, there are only a limited number of therapeutic options, including emicizumab (for hemophilia A only), immune tolerance induction (ITI), and bypassing agents, such as rFVIIa (NovoSeven and SevenFact) and activated prothrombin complex concentrate (aPCC, FEIBA).

Investigational Uses

- The use of non-factor hemophilia A and B prophylactic products (as listed in Table 1) for indications other than those listed in the coverage criteria above are considered investigational. Trials in various settings are ongoing.
- There are no published clinical trials evaluating the safety or efficacy of non-factor hemophilia A and B prophylactic products (as listed in Table 1) being used in combination with one another or with emicizumab (Hemlibra).

Appendices

Appendix 1: Clinical Reasons Extended Half-Life (EHL) Factor Products Are Not Appropriate

Severe life-threatening hypersensitivity reaction, including anaphylaxis to factor proteins.
Inadequate venous access for prophylactic IV therapy due to comorbidities or age.
Unable to self-administer IV therapy.

Appendix 2: Extended Half-life (EHL) Factor VIII Products

Hemophilia A – Factor VIII Products		
Medication	**Recombinant or Plasma-Derived**	**FDA-recommended Prophylactic Dosing**
Adynovate[31]	Recombinant	>12 years old: Up to 50 IU/kg two times per week. <12 years old: Initially up to 55 IU/kg two times per week with a maximum of 70 IU/kg.
Afstyla*[24]	Recombinant	>12 years old: Up to 50 IU/kg 2 to 3 times per week. <12 years old: Up to 50 IU/kg every other day.
Altuviiio	Recombinant	Up to 50 IU/kg once weekly.
Eloctate[32]	Recombinant	>6 years old: Up to 65 IU/kg every 3 to 5 days. <6 years old: Up to 65 IU/kg every 3 to 5 days. More frequent or higher doses (up to 80 IU/kg) may be required.
Jivi[33]	Recombinant	>12 years old: Up to 40 IU/kg twice weekly. <12 years old: Not approved for use in this age group.
Esperoct[34]	Recombinant	>12 years old: Up to 50 IU/kg every 4 days. <12 years old: Up to 65 IU/kg twice weekly.

* denotes lower cost factor product

Appendix 3: Extended Half-life (EHL) Factor IX Products

Hemophilia B- Factor IX Products		
Medication	**Recombinant or Plasma-Derived**	**FDA- recommended Prophylactic Dosing**
Alprolix[35]	Recombinant	>12 years old: Up to 50 IU/kg once weekly or 100 IU/kg once every 10 days. <12 years old: Up to 60 IU/kg once weekly.
Idelvion[36]	Recombinant	>12 years old: Up to 40 IU/kg once weekly. <12 years old: Up to 55 IU/kg once weekly.
Rebinyn[37]	Recombinant	Not indicated for prophylaxis.

Cross References

Hemlibra, emicizumab-kxwh, Medication Policy Manual, Policy No. 539
Blood Factors for Hemophilia A, Extended Half-Life (EHL) Products, Medication Policy Manual, Policy No. 549
Blood Factors for Hemophilia B, Extended Half-Life (EHL) Products, Medication Policy Manual, Policy No. 550

Codes	Number	Description
HCPCS	J3590	Unclassified biologics

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15. Xyntha [prescribing information]. Philadelphia, PA: Wyeth Pharmaceuticals: Wyeth Pharmaceuticals.
16. Kogenate [prescribing information]. Whippany, NJ: Bayer: Bayer.
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18. Helixate [prescribing information]. Kankakee, IL: CSL Behring: CSL Behring.
19. Hemofil M [prescribing information]. Westlake Village, CA: Shire: Shire.
20. Monoclate-P [prescribing information]. Kankakee, IL: CSL Behring: CSL Behring.
21. Alphanate [prescribing information]. Los Angeles, CA: Grifols: Grifols.
22. Koate-DVI [prescribing information]. Los Angeles, CA: Grifols: Grifols.
23. Humate-P [prescribing information]. Kankakee, IL: CSL Behring: CSL Behring.
24. Afstyla [Prescribing Information]. Kankakee, IL: CSL Behring: CSL Behring.
25. BeneFIX [prescribing information]. Philadelphia, PA: Wyeth: Wyeth.
26. Ixinity [prescribing information]. Berwyn, PA: Aptevo BioTherapeutics: Aptevo BioTherapeutics.
27. Rixubis [prescribing information]. Westlake Village, CA: Shire: Shire.
28. AlphaNine SD [prescribing information]. Los Angeles, CA: Grifols Biologicals: Grifols Biologicals.
29. Mononine [prescribing information]. Kankakee, IL: CSL Behring: CSL Behring.

30. Profilnine [prescribing information]. Los Angeles, CA: Grifols Biologicals: Grifols Biologicals.
31. Adynovate [Prescribing Information]. Westlake Village, CA: Shire: Shire.
32. Eloctate (antihemophilic factor recombinant, FC fusion) [Prescribing Information]. Waltham, MA: Sanofi.
33. Jivi [Prescribing Information]. Whippany, NJ: Bayer: Bayer.
34. Esperoct [Prescribing Information]. Plainsboro, NJ: Novo Nordisk: Novo Nordisk.
35. Alprolix (coagulation factor IX recombinant FC fusion) [Prescribing Information]. Waltham, MA: Sanofi.
36. Idelvion [prescribing information]. Kankakee, IL: CSL Behring: CSL Behring.
37. Rebinyn [prescribing information]. Plainsboro, NJ: Novo Nordisk: Novo Nordisk.

Revision History

Revision Date	Revision Summary
3/6/2025	New policy effective 4/15/2025

Drug names identified in this policy are the trademarks of their respective owners.

Regence

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UMP Medication Policy Manual

Policy No: dru900

Topic: Provider-administered drugs for chronic inflammatory diseases (for UMP plans)

Date of Origin: January 1, 2020

- Cimzia (certolizumab lyophilized powder vial)
- Cosentyx (secukinumab intravenous)
- Entyvio (vedolizumab)
- Ilumya (tildrakizumab-asmn)
- Omvoh (mirkizumab)
- Orencia (abatacept intravenous)
- Simponi Aria (golimumab intravenous)
- Skyrizi (risankizumab)
- Spevigo (spesolimab)
- Tocilizumab (Actemra; biosimilars Tofidence, Tyenne)
- Tremfya (guselkumab)
- Ustekinumab (Stelara; biosimilars Pyzchiva, Selarsdi, Wezlana)

Committee Approval Date: December 16, 2024

Next Review Date: 2025

Effective Date: January 1, 2025

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Therapies included in this policy are used to treat a group of diseases that may be caused or worsened by an overactive immune system such as rheumatoid arthritis, psoriasis, and ulcerative colitis.

This policy applies to the Washington State Health Care Authority (HCA) Uniform Medical Plan (UMP) only. The UMP is a self-funded health plan offered through the Washington State HCA's Public Employees Benefits Board (PEBB) Program and School Employees Benefits Board (SEBB) Program and administered by Regence BlueShield.

Table of Contents

Disease Modifying Antirheumatic Drug (DMARD)			
Targeted DMARD			Conventional synthetic DMARDs
Tumor necrosis factor inhibitor (TNF) biologics	Non-tumor necrosis factor inhibitor (non-TNF inhibitor) biologics	Targeted synthetic DMARD (tsDMARD)	
	IL-6 Inhibitors IL-17 Inhibitors IL 12/23 and IL-23 Inhibitors Integrin inhibitors Other mechanisms of action: IL-I rituximab, abatacept	JAK Inhibitors PDE-4 Inhibitors	

Drug List:		
TNF inhibitors		- Adalimumab (Humira; biosimilars Abrilada, Amjevita, Cyltezo, Hadlima, Hulio, Hyrimoz, Idacio, Simlandi, Yuflyma, Yusimry; unbranded: adalimumab-adaz, adalimumab-adbm, adalimumab-ryvk) - Cimzia (certolizumab pre-filled syringes for self-administration or vials for provider-administration) - Enbrel (etanercept) - Etanercept biosimilars (Erelzi, Eticovo) - Simponi/Simponi Aria (golimumab) IV or SC - Remicade (infliximab) - Infliximab products (Inflectra, Ixifi, Renflexis, Avsola, unbranded product, Zymfentra)
IL-6 inhibitors		- Kevzara (sarilumab) - Tocilizumab biosimilars (Tofidence, Tyenne) IV or SC
IL-17 Inhibitors		- Siliq (brodalumab) - Taltz (ixekizumab) - Cosentyx (secukinumab) IV or SC - Bimzelx (bimekizumab-bkzx) IL-17A, IL-17F inhibitor
IL-23 inhibitors		- Tremfya (guselkumab) - Skyrizi (risankizumab) - Ilumya (tildrakizumab-asmn) - Omvoh (mirikizumab-mrkz)
IL-12, IL-23 inhibitors		- Ustekinumab (Stelara; biosimilars Pyzchiva, Selarsdi, Wezlana)
IL-36 inhibitors		- Spevigo (spesolimab)
Integrin Inhibitors		- Tysabri (natalizumab) - Entyvio (vedolizumab)
Other non-TNF inhibitor biologics	T-lymphocyte inhibitor	- Orencia (abatacept) IV or SC
	B-lymphocyte depleter	- Rituximab (Rituxan Hycela, Rituxan; biosimilars Riabni, Ruxience, Truxima) [a]
	IL-1	- Kineret (anakinra) - Ilaris (canakinumab)
JAK Inhibitors		- Olumiant (baricitinib) - Tofacitinib (Xeljanz/Xeljanz XR) - Rinvoq (upadacitinib) - Sotyktu (deucravacitinib)
PDE-4 Inhibitor		- Otezla (apremilast)
S1P receptor modulator		- Velsipity (etrasimod)
Conventional immunomodulators (also referred to as conventional synthetic DMARDs) (see appendix 2, for complete		- Azathioprine (generic, Imuran) - 6-mercaptopurine (generic, 6-MP) - Methotrexate (generic, MTX)

list)	- Hydroxychloroquine (HCQ; generic, Plaquenil) - Leflunomide (generic, Arava) - Mycophenolate (MMF; generic, CellCept, Myfortic) - Cyclosporine (CSA; Gengraf, Neoral, Sandimmune) - Tacrolimus (generic, Prograf) - 5 ASAs [sulfasalazine (generic, SSZ), mesalamine, balsalazide] - Acitretin (generic, Accutane)

Policy/Criteria

Most contracts require pre-authorization approval of drugs for chronic inflammatory diseases prior to coverage.

I. **For self-administered therapies**, please refer to coverage policies administered by ArrayRx.

II. Continuation of therapy (COT): Provider-administered therapies in this policy may be considered medically necessary for COT when criteria A and B below are met.

A. One of the following (1, 2, or 3):

1. For diagnoses NOT listed in the coverage criteria below, full policy criteria must be met for coverage.

OR

2. For diagnoses listed in the coverage criteria below, criteria a and b must be met:

a. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

b. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

3. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

AND

B. Site of care administration requirements are met [refer to Medication Policy Manual, Site of Care Review, dru408].

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

III. New starts (treatment-naïve patients): Provider-administered therapies in the policy may be considered medically necessary when the criteria below are met.

A. Acute Graft Versus Host Disease, Prophylaxis

1. Provider-administered therapies may be considered medically necessary when criteria a through c below are met.

FOR UMP MEMBERS:	
Preferred Self-Administered Options Refer to ArrayRx.	Refer to coverage policies administered by ArrayRx.
Non-Preferred Self-Administered Options Refer to ArrayRx.	Refer to coverage policies administered by ArrayRx.
Provider-Administered Options	Orencia (abatacept) IV

a. Abatacept will be used for **prophylaxis** of **acute graft versus host disease** (aGVHD).

AND

b. Patient will undergo a hematopoietic cell transplant (HCT) from an unrelated donor (either 8/8 HLA matched or 7/8 HLA mismatch).

AND

c. Abatacept will be used in combination with methotrexate and a calcineurin inhibitor (cyclosporine or tacrolimus).

B. Ankylosing Spondylitis (AS)

1. For provider-administered therapies, site of care administration requirements must be met [refer to Medication Policy Manual, Site of Care Review, dru408].
2. For infliximab products: Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620.
3. Other provider-administered therapies may be considered medically necessary when criteria a and b below are met.

FOR UMP MEMBERS:	
Preferred Self-Administered Options Refer to ArrayRx.	Refer to coverage policies administered by ArrayRx.
Non-Preferred Self-Administered Options Refer to ArrayRx.	Refer to coverage policies administered by ArrayRx.
Infliximab Products	Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620. Preferred: • Avsola • Inflectra (infliximab) Non-preferred: • Remicade (infliximab) • Other infliximab biosimilars (Ixifi, Renflexis) • Unbranded Janssen infliximab product
Other Provider-Administered Options	• Cimzia (certolizumab) vial • Simponi Aria (golimumab) IV • Cosentyx (secukinumab) IV

a. A diagnosis of **axial spondyloarthritis (axSpA)**, including **ankylosing spondylitis** (AS), is established by or in consultation with a specialist in rheumatology.

AND

b. There is clinical documentation that treatment with **at least TWO** preferred self-administered therapies were not effective after at least a 12-week treatment course unless each were not tolerated or are contraindicated (including, but not limited to, contraindications listed in *Appendix 6*).

C. Antibody Mediated Rejection (AMR) of Transplant (Solid Organ)

1. Preferred provider-administered therapies may be considered medically necessary when criteria a and b below are met.

2. Other provider-administered therapies may be considered medically necessary when criteria a through c below are met.

FOR UMP MEMBERS:	
Preferred Self-Administered Options Refer to ArrayRx.	Refer to coverage policies administered by ArrayRx.
Non-Preferred Self-Administered Options Refer to ArrayRx.	Refer to coverage policies administered by ArrayRx.
Preferred Provider-Administered Options	• Tyenne (tocilizumab-aazg) IV
Other Provider-Administered Options	• Actemra (tocilizumab) IV • Tofidence (tocilizumab-bavi) IV

a. Medication will be used for **prevention of antibody (Ab)-mediated rejection**: Prior to solid organ transplant and in the peri-operative period, for patients at high risk for Ab-mediated rejection, including highly sensitized patients, and those receiving an ABO-incompatible organ **OR Treatment of antibody-mediated rejection** (a.k.a. vascular rejection, humoral rejection): following solid organ transplant and confirmed by either biopsy or presence of panel reactive antibodies (PRAs).

AND

b. Treatment with immunoglobulin (IVIG), plasma exchange/pheresis (PLEX), and rituximab has been ineffective or is contraindicated.

AND

c. There is clinical documentation that treatment with all preferred provider-administered therapies were not effective unless each were not tolerated or are contraindicated.

D. Non-Radiographic Axial Spondyloarthritis (NR-axSpA)

1. For provider-administered therapies, site of care administration requirements must be met [refer to Medication Policy Manual, Site of Care Review, dru408].

2. Provider-administered therapies may be considered medically necessary when criteria a and b below are met.

3. Provider-administered biosimilar reference products may be considered medically necessary when criteria a and b below are met.

FOR UMP MEMBERS:	
Preferred Self-Administered Options Refer to ArrayRx.	Refer to coverage policies administered by ArrayRx.
Non-Preferred Self-Administered Options Refer to ArrayRx.	Refer to coverage policies administered by ArrayRx.
Provider-Administered Options	• Cimzia (certolizumab) vial • Cosentyx (secukinumab) IV
a. A diagnosis of **non-radiographic axial SpA** (NR-axSpA) is established by or in consultation with a specialist in rheumatology. **AND** **b.** Treatment with **at least ONE** preferred self-administered therapy was not effective after at least a 12-week treatment course unless each were not tolerated or are contraindicated (including, but not limited to, contraindications listed in *Appendix 6*).	

E. Chronic Plaque Psoriasis (PsO)

1. For provider-administered therapies, site of care administration requirements must be met [refer to Medication Policy Manual, Site of Care Review, dru408].

2. For infliximab products: Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620.

3. Preferred provider-administered therapies may be considered medically necessary when criteria a and b below are met.

4. Other provider-administered therapies may be considered medically necessary when criteria a through c below are met.

FOR UMP MEMBERS:	
Preferred Self-Administered Options Refer to ArrayRx.	Refer to coverage policies administered by ArrayRx.
Non-Preferred Self-Administered Options Refer to ArrayRx.	Refer to coverage policies administered by ArrayRx.
Infliximab Products	Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620. Preferred: • Avsola (infliximab) • Inflectra (infliximab) Non-preferred: • Remicade (infliximab) • Other infliximab biosimilars (Ixifi, Renflexis) • Unbranded Janssen infliximab product
Preferred Provider-Administered Options	• Stelara (ustekinumab)
Other Provider-Administered Options	• Cimzia (certolizumab) vial • Ilumya (tildrakizumab-asmn) • Ustekinumab biosimilars (Pyzchiva, Selarsdi, Wezlana)

a. A diagnosis of **chronic plaque psoriasis** (PsO) is established by or in consultation with a specialist in dermatology or rheumatology.

AND

b. One of the following criterion i, ii, or iii below is met.

i. There is involvement of ≥ 10% of the body surface area (BSA) OR there is significant functional disability due to PsO.

OR

ii. Treatment with phototherapy (for example, UVB) or photochemotherapy was not effective, not tolerated, or is contraindicated (such as lesions on the face, scalp, hands, feet, nailbeds, or groin area; see *Appendix 1*).

OR

iii. Treatment with at least one conventional agent was not effective after at least 6 to 12 weeks of treatment, or not tolerated, unless all are contraindicated. Conventional agents for the treatment of PsO include: acitretin, anthralin, calcipotriene, calcitriol, coal tar products, cyclosporine, methotrexate, pimecrolimus, tacrolimus, tazarotene, or a topical corticosteroid.

AND

c. There is clinical documentation that treatment with **at least TWO** preferred self-administered therapies were not effective after at least a 12-week treatment course unless each were not tolerated or are contraindicated (including, but not limited to, contraindications listed in *Appendix 6*).

F. Crohn's Disease (CD)

1. **Site of Care Requirements:** For provider-administered therapies, site of care administration requirements must be met [refer to Medication Policy Manual, Site of Care Review, dru408 [Stelara (ustekinumab) and Skyrizi (risankizumab) do not require Site of Care Review].

2. **Diagnostic Criteria:** A diagnosis of **Crohn's disease** (CD) established by or in consultation with a specialist in gastroenterology.

3. **Severity Criteria:** Either criterion a or b below is met.

a. At least one of the following criteria 1 through 6 below are met.

1. Fistulizing Crohn's disease.

2. Previous hospitalization for Crohn's disease.

3. Extensive anatomic involvement.

4. Deep ulcers.

5. Prior surgical resection.

6. Stricturing and/or penetrating behavior.

OR

b. Acute treatment of an exacerbation when at least one of criterion 1, 2, or 3 below, is met.

1. Treatment with an adequate course of corticosteroids (for example, prednisone 40 to 60 mg/day, oral budesonide 9 mg/day, or budesonide rectal for 7 to 14 days) has been ineffective or is contraindicated.

OR

2. The patient has been unable to taper an adequate course of corticosteroids without experiencing worsening of disease.

OR

3. The patient is experiencing breakthrough disease (e.g., active disease flares) while stabilized for at least 8 weeks on a conventional immunomodulator. Conventional immunomodulators for CD include azathioprine, mercaptopurine, methotrexate, balsalazide, mesalamine, cyclosporine, and sulfasalazine.

FOR UMP MEMBERS:		
Product Group	**Products**	**Criteria Requirements**
Preferred Self-Administered Options	Refer to ArrayRx.	Refer to coverage policies administered by ArrayRx.
Non-Preferred Self-Administered Options	Refer to ArrayRx.	Refer to coverage policies administered by ArrayRx.
Preferred Provider-Administered Options	• Entyvio (vedolizumab) • Skyrizi (risankizumab) • Stelara (ustekinumab)	**1.** Site of Care Requirements *(Entyvio only)* **2.** Diagnostic Criteria **3.** Severity Criteria
	• Avsola (infliximab) • Inflectra (infliximab)	Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620.
Non-Preferred Provider-Administered Options	• Cimzia (certolizumab) vial • Ustekinumab biosimilars (Pyzchiva, Selarsdi, Wezlana)	**1.** Site of Care Requirements *(Cimzia only)* **2.** Diagnostic Criteria **3.** Severity Criteria **4.** Treatment with **at least TWO** preferred self-administered therapies has been not effective after at least a 12-week treatment course unless each were not tolerated or are contraindicated (including, but not limited to, contraindications listed in *Appendix 6*).
Non-preferred infliximab Products	• Infliximab biosimilars (Ixifi, Renflexis) • Remicade (infliximab) • Unbranded Janssen infliximab product	Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620.

G. Cryopyrin-Associated Periodic Syndrome (CAPS)

1. For self-administered therapies, please refer to coverage policies administered by ArrayRx.

FOR UMP MEMBERS:	
Preferred Self-Administered Options Refer to ArrayRx.	Refer to coverage policies administered by ArrayRx.
Non-Preferred Self-Administered Options Refer to ArrayRx.	Refer to coverage policies administered by ArrayRx.
Provider-Administered Options	Refer to Interleukin-1 Antagonists, Medication Policy Manual, Policy No. dru677

H. Cytokine Release Syndrome (CRS)

1. Preferred provider-administered therapies may be considered medically necessary when criterion a below is met.

2. Other provider-administered therapies may be considered medically necessary when criteria a and b below are met.

FOR UMP MEMBERS:	
Preferred Self-Administered Options Refer to ArrayRx.	Refer to coverage policies administered by ArrayRx.
Non-Preferred Self-Administered Options Refer to ArrayRx.	Refer to coverage policies administered by ArrayRx.
Preferred Provider-Administered Options	• Tyenne (tocilizumab-aazg) IV
Other Provider-Administered Options	• Actemra (tocilizumab) IV • Tofidence (tocilizumab-bavi) IV
a. Medication will be used for **cytokine release syndrome** (CRS). **AND** **b.** There is clinical documentation that treatment with all preferred provider-administered therapies were not effective unless each were not tolerated or are contraindicated.	

I. Enthesitis-related Arthritis (ERA)

1. For provider-administered therapies, site of care administration requirements must be met [refer to Medication Policy Manual, Site of Care Review, dru408].

2. Provider-administered therapies may be considered medically necessary when criterion a below is met.

FOR UMP MEMBERS:	
Preferred Self-Administered Options Refer to ArrayRx.	Refer to coverage policies administered by ArrayRx.
Non-Preferred Self-Administered Options Refer to ArrayRx.	Refer to coverage policies administered by ArrayRx.
Provider-Administered Options	
a. A diagnosis of **enthesitis-related arthritis** (ERA) is established by or in consultation with a specialist in rheumatology.	

J. Generalized Pustular Psoriasis (GPP)

1. For infliximab products: Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/ Reference Products, dru620.

2. Other provider-administered therapies may be considered medically necessary when criteria a and b below are met.

FOR UMP MEMBERS:	
Preferred Self-Administered Options Refer to ArrayRx.	Refer to coverage policies administered by ArrayRx.
Non-Preferred Self-Administered Options Refer to ArrayRx.	Refer to coverage policies administered by ArrayRx.
Infliximab Products	Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620. Preferred: • Avsola • Inflectra (infliximab) Non-preferred: • Remicade (infliximab) • Other infliximab biosimilars (Ixifi, Renflexis) • Unbranded Janssen infliximab product
Other Provider-Administered Options	Spevigo (spesolimab)

a. A diagnosis of **generalized pustular psoriasis (GPP)** established by or in consultation with a specialist in dermatology.

AND

b. One of the following criterion i or ii below is met.

i. **Treatment of GPP flare (IV formulation only)** when all of the following are met:

1. Documentation of disease progression despite usual treatment with cyclosporine OR infliximab unless not tolerated, or both are contraindicated.
2. There is involvement of ≥ 5% of body surface area (BSA) with erythema and the presence of pustules.

OR

ii. **Maintenance treatment for GPP (SC loading dose only)** when all of the following are met:

1. History of at least two moderate-to-severe flares, with at least one associated with fever, elevated C-reactive protein level, elevated white blood cell count, asthenia, or myalgia.
2. Currently not experiencing a flare.
3. Treatment with acitretin and methotrexate for at least eight weeks has been ineffective or not tolerated, unless both are contraindicated.

K. Giant Cell Arteritis (GCA)

1. For provider-administered therapies, site of care administration requirements must be met [refer to Medication Policy Manual, Site of Care Review, dru408].
2. Preferred provider-administered therapies may be considered medically necessary when criteria a and b below are met.
3. Other provider-administered therapies may be considered medically necessary when criteria a through c below are met.

FOR UMP MEMBERS:	
Preferred Self-Administered Options Refer to ArrayRx.	Refer to coverage policies administered by ArrayRx.
Non-Preferred Self-Administered Options Refer to ArrayRx.	Refer to coverage policies administered by ArrayRx.
Preferred Provider-Administered Options	• Tyenne (tocilizumab-aazg) IV
Other Provider-Administered Options	• Actemra (tocilizumab) IV • Tofidence (tocilizumab-bavi) IV

a. A diagnosis of **giant cell arteritis** (GCA) when established by or in consultation with a specialist in rheumatology.

AND

b. Requested medication will be given in combination with high-dose corticosteroids (prednisone 20 to 60 mg per day or equivalent) unless contraindicated or not tolerated.

AND

c. There is clinical documentation that treatment with all preferred provider administered options were not effective unless each were not tolerated or are contraindicated.

L. Hidradenitis Suppurativa (HS)

1. For provider-administered therapies, site of care administration requirements must be met [refer to Medication Policy Manual, Site of Care Review, dru408].

2. Provider-administered therapies may be considered medically necessary when criteria a and b below are met.

3. For infliximab products: Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620.

FOR UMP MEMBERS:	
Preferred Self-Administered Options Refer to ArrayRx.	Refer to coverage policies administered by ArrayRx.
Non-Preferred Self-Administered Options Refer to ArrayRx.	Refer to coverage policies administered by ArrayRx.
Infliximab Products	Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620. Preferred: • Avsola • Inflectra (infliximab) Non-preferred: • Remicade (infliximab) • Other infliximab biosimilars (Ixifi, Renflexis) • Unbranded Janssen infliximab product

a. A diagnosis of **hidradenitis suppurativa** (HS) is established by or in consultation with a specialist in dermatology.

AND

b. Treatment with at least one conventional agent was not effective after 12 weeks, not tolerated, or all are contraindicated. Conventional agents for the treatment of HS include topical antibiotics, systemic antibiotics (e.g., oral tetracyclines, clindamycin, rifampin, moxifloxacin, metronidazole), intralesional corticosteroids (e.g., triamcinolone), hormonal therapies (e.g., oral contraceptives, spironolactone), cyclosporine, finasteride, metformin, or oral retinoids.

M. Immune-Mediated Colitis

1. Provider-administered therapies may be considered medically necessary when criteria a and b below are met.

2. For infliximab products: Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620.

FOR UMP MEMBERS:	
Preferred Self-Administered Options Refer to ArrayRx.	Refer to coverage policies administered by ArrayRx.
Non-Preferred Self-Administered Options Refer to ArrayRx.	Refer to coverage policies administered by ArrayRx.
Infliximab Products	Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620. Preferred: • Avsola (infliximab) • Inflectra (infliximab) Non-preferred: • Remicade (infliximab) • Other infliximab biosimilars (Ixifi, Renflexis) • Unbranded Janssen infliximab product
Provider-Administered Options	Entyvio (vedolizumab)

a. A diagnosis of **colitis** due to Yervoy (ipilimumab) or an anti-PD1/PD-L1 agent [e.g., Tecentriq (atezolizumab), Bavencio (avelumab), Libtayo (cemiplimab), Jemperli (dostarlimab), Imfinzi (durvalumab), Opdivo (nivolumab), or Keytruda (pembrolizumab) or Zynyz (retifanlimab)].[a]

AND

b. Treatment with an adequate course of corticosteroids (for example, prednisone 40 to 60 mg/day, oral budesonide 9 mg/day, or budesonide rectal for 7 days) has been ineffective or is contraindicated.

[a] Or as listed on the FDA.gov website.

N. Polyarticular Juvenile Idiopathic Arthritis (PJIA)

1. For provider-administered therapies, site of care administration requirements must be met [refer to Medication Policy Manual, Site of Care Review, dru408].

2. For infliximab products: Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620.

3. Preferred provider-administered therapies may be considered medically necessary when criteria a through c below are met.

4. Other provider-administered therapies may be considered medically necessary when criteria a through d below are met.

FOR UMP MEMBERS:	
Preferred Self-Administered Options Refer to ArrayRx.	Refer to coverage policies administered by ArrayRx.
Non-Preferred Self-Administered Options Refer to ArrayRx.	Refer to coverage policies administered by ArrayRx.
Infliximab Products	Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620. Preferred: • Avsola (infliximab) • Inflectra (infliximab) Non-preferred: • Remicade (infliximab) • Other infliximab biosimilars (Ixifi, Renflexis) • Unbranded Janssen infliximab product
Preferred Provider-Administered Options	• Orencia (abatacept) IV • Simponi Aria (golimumab IV) • Tyenne (tocilizumab-aazg) IV
Other Provider-Administered Options	• Actemra (tocilizumab) IV • Tofidence (tocilizumab-bavi) IV

a. A diagnosis of **polyarticular juvenile idiopathic arthritis** (PJIA) is established by or in consultation with a specialist in rheumatology.

AND

b. Treatment with a conventional immunomodulator (such as leflunomide, methotrexate, or sulfasalazine) was not effective after at least 6 weeks, or that a conventional immunomodulator was not tolerated, or all conventional immunomodulators are contraindicated.

AND

c. There is clinical documentation that treatment with **at least TWO** preferred self-administered therapies was not effective after at least a 12-week treatment course unless each were not tolerated or are contraindicated (including, but not limited to, contraindications listed in *Appendix 6*).

AND

d. There is clinical documentation that treatment with all preferred provider-administered **tocilizumab options** was not effective after at least a 12-week treatment course unless each were not tolerated or are contraindicated.

O. Psoriatic Arthritis (PsA)

1. For provider-administered therapies, site of care administration requirements must be met [refer to Medication Policy Manual, Site of Care Review, dru408].
2. For infliximab products: Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620.
3. Preferred provider-administered therapies may be considered medically necessary when criterion a below is met.
4. Other provider-administered therapies may be considered medically necessary when criteria a and b below are met.

FOR UMP MEMBERS:	
Preferred Self-Administered Options Refer to ArrayRx.	Refer to coverage policies administered by ArrayRx.
Non-Preferred Self-Administered Options Refer to ArrayRx.	Refer to coverage policies administered by ArrayRx.
Infliximab Products	Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620. Preferred: • Avsola (infliximab) • Inflectra (infliximab) Non-preferred: • Remicade (infliximab) • Other infliximab biosimilars (Ixifi, Renflexis) • Unbranded Janssen infliximab product
Preferred Provider-Administered Options	• Stelara (ustekinumab)
Other Provider-Administered Options	• Orencia (abatacept) IV • Cimzia (certolizumab) vial • Simponi Aria (golimumab) IV • Cosentyx (secukinumab) IV • Ustekinumab biosimilars (Pyzchiva, Selarsdi, Wezlana)
a. A diagnosis of **psoriatic arthritis** (PsA) when established by or in consultation with a specialist in dermatology or rheumatology. **AND** **b.** There is clinical documentation that treatment with **at least TWO** preferred self-administered therapies were not effective after at least a 12-week treatment course unless each were not tolerated or are contraindicated (including, but not limited to, contraindications listed in *Appendix 6*).	

P. Rheumatoid Arthritis (RA)

1. For provider-administered therapies, site of care administration requirements must be met [refer to Medication Policy Manual, Site of Care Review, dru408].

2. For infliximab products: Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620.

3. Preferred provider-administered therapies may be considered medically necessary when criteria a through c below are met.

4. Other provider-administered therapies may be considered medically necessary when criteria a through d below are met.

FOR UMP MEMBERS:	
Preferred Self-Administered Options Refer to ArrayRx.	Refer to coverage policies administered by ArrayRx.
Non-Preferred Self-Administered Options Refer to ArrayRx.	Refer to coverage policies administered by ArrayRx.
Infliximab Products	Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620. Preferred: • Avsola (infliximab) • Inflectra (infliximab) Non-preferred: • Remicade (infliximab) • Other infliximab biosimilars (Ixifi, Renflexis) • Unbranded Janssen infliximab product
Preferred Provider-Administered Options	• Orencia (abatacept) IV • Cimzia (certolizumab) vial • Simponi Aria (golimumab IV) • Tyenne (tocilizumab-aazg) IV
Other Provider-Administered Options	• Actemra (tocilizumab) IV • Tofidence (tocilizumab-bavi) IV

a. A diagnosis of **rheumatoid arthritis** (RA) is established by or in consultation with a specialist in rheumatology (see *Appendix 3*).

AND

b. Treatment with a conventional synthetic DMARD (csDMARD) was not effective after at least a 6 to 12-week treatment course based on one or more of the assessment components listed in *Appendix 4*, or that a csDMARD was not tolerated or all csDMARDs are contraindicated. csDMARDs for RA include hydroxychloroquine, leflunomide, methotrexate, and sulfasalazine.

AND

c. There is clinical documentation that treatment with **at least TWO** preferred self-administered therapies were not effective after at least a 12-week treatment course unless each were not tolerated or are contraindicated (including, but not limited to, contraindications listed in *Appendix 6*).

AND

d. There is clinical documentation that treatment with all preferred provider-administered **tocilizumab options** were not effective after at least a 12-week treatment course unless each were not tolerated or are contraindicated.

Q. Takayasu Arteritis

1. For provider-administered therapies, site of care administration requirements must be met [refer to Medication Policy Manual, Site of Care Review, dru408].
2. For infliximab products: Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620.
3. Preferred provider-administered options may be considered medically necessary when criteria a and b below are met.
4. Other provider-administered options may be considered medically necessary when criteria a through c below are met.

FOR UMP MEMBERS:	
Preferred Self-Administered Options Refer to ArrayRx.	Refer to coverage policies administered by ArrayRx.
Non-Preferred Self-Administered Options Refer to ArrayRx.	Refer to coverage policies administered by ArrayRx.
Infliximab Products	Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620. Preferred: • Avsola (infliximab) • Inflectra (infliximab) Non-preferred: • Remicade (infliximab) • Other infliximab biosimilars (Ixifi, Renflexis) • Unbranded Janssen infliximab product
Preferred Provider-Administered Options	• Tyenne (tocilizumab-aazg) IV
Other Provider-Administered Options	• Actemra (tocilizumab) IV • Tofidence (tocilizumab-bavi) IV

a. A diagnosis of **Takayasu Arteritis** is established by or in consultation with a specialist in rheumatology or immunology.

AND

b. One of the following i or ii below are met.

i. The patient has been unable to taper corticosteroids without experiencing worsening of disease (e.g., unable to achieve doses of 15-20 mg per day or less of prednisone or equivalent after 8 weeks).

OR

ii. The patient is experiencing breakthrough disease (for example, relapses or active disease flares) while stabilized on a conventional immunomodulators, for at least 8 weeks.

AND

c. There is clinical documentation that treatment with all preferred provider-administered therapies were not effective unless each were not tolerated or are contraindicated.

R. Systemic Juvenile Idiopathic Arthritis (SJIA; Still's disease)

1. For provider-administered therapies, site of care administration requirements must be met [refer to Medication Policy Manual, Site of Care Review, dru408].
2. Preferred provider-administered therapies may be considered medically necessary when criteria a through d below are met.
3. Other provider-administered therapies may be considered medically necessary when criteria a through e below are met.

FOR UMP MEMBERS:	
Preferred Self-Administered Options Refer to ArrayRx.	Refer to coverage policies administered by ArrayRx.
Non-Preferred Self-Administered Options Refer to ArrayRx.	Refer to coverage policies administered by ArrayRx.
Preferred Provider-Administered Options	• Tyenne (tocilizumab-aazg) IV
Other Provider-Administered Options	• Actemra (tocilizumab) IV • Tofidence (tocilizumab-bavi) IV

a. A diagnosis of **systemic juvenile idiopathic arthritis** (SJIA; Still's disease) is established by or in consultation with a specialist in rheumatology.

AND

b. There is disease activity greater than 6 weeks.

AND

c. One of the following i or ii below is met.

i. Treatment with at least one oral conventional agent was not effective after 12 weeks, not tolerated, or is contraindicated. Conventional agents for the treatment of SJIA include azathioprine, cyclosporine, leflunomide, methotrexate, systemic corticosteroids, or tacrolimus.

OR

ii. Treatment with at least one NSAID (e.g., ibuprofen, celecoxib) was not effective after 4 weeks, not tolerated, or all are contraindicated.

AND

d. There is clinical documentation that treatment with **at least ONE** preferred self-administered therapy was not effective after at least a 12-week treatment course unless each were not tolerated or are contraindicated (including, but not limited to, contraindications listed in *Appendix 6*).

AND

e. There is clinical documentation that treatment with all preferred provider-administered therapies were not effective after at least a 12-week treatment course unless each were not tolerated or are contraindicated.

S. Ulcerative Colitis (UC)

1. **Site of Care Requirements**: For provider-administered therapies, site of care administration requirements are met [refer to Medication Policy Manual, Site of Care Review, dru408].
2. **Diagnostic Criteria**: A diagnosis of ulcerative colitis (UC) when established by or in consultation with a specialist in gastroenterology.
3. **Severity Criteria**: At least one of the following criterion (a, b, or c) below is met.
   - **a.** Treatment with an adequate course of corticosteroids (for example, prednisone 40 to 60 mg/day, oral budesonide 9 mg/day, or budesonide rectal for 7 to 14 days) was ineffective or is contraindicated; **OR**
   - **b.** The patient has been unable to taper an adequate course of corticosteroids without experiencing worsening of disease; **OR**
   - **c.** The patient is experiencing breakthrough disease (for example, active disease flares) while stabilized on a conventional immunomodulators, for at least two months. Conventional immunomodulators for UC include azathioprine, balsalazide, cyclosporine, mercaptopurine, mesalamine, and sulfasalazine.

FOR UMP MEMBERS:		
Product Group	**Products**	**Criteria Requirements**
Preferred Self-Administered Options	Refer to ArrayRx.	Refer to coverage policies administered by ArrayRx.
Non-Preferred Self-Administered Options	Refer to ArrayRx.	Refer to coverage policies administered by ArrayRx.
Preferred Provider-Administered Options	• Entyvio (vedolizumab) • Skyrizi (risankizumab) • Stelara (ustekinumab) • Tremfya (guselkumab)	**1.** Site of Care Requirements **2.** Diagnostic Criteria **3.** Severity Criteria
	• Avsola (infliximab) • Inflectra (infliximab)	Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620.
Non-Preferred Provider-Administered Options	• Omvoh (mirikizumab) • Ustekinumab biosimilars (Pyzchiva, Selarsdi, Wezlana)	**1.** Diagnostic Criteria **2.** Severity Criteria **3.** Treatment with **ALL** preferred self-administered therapies has been not effective after at least a 12-week treatment course unless each were not tolerated or are contraindicated (including, but not limited to, contraindications listed in *Appendix 6*).
Non-preferred infliximab Products	• Infliximab biosimilars (Ixifi, Renflexis) • Remicade (infliximab) • Unbranded Janssen infliximab product	Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620.

T. Uveitis

1. For provider-administered therapies, site of care administration requirements must be met [refer to Medication Policy Manual, Site of Care Review, dru408].

2. Provider-administered therapies may be considered medically necessary when criteria a through c below are met.

3. For infliximab products: Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620.

FOR UMP MEMBERS:	
Preferred Self-Administered Options Refer to ArrayRx.	Refer to coverage policies administered by ArrayRx.
Non-Preferred Self-Administered Options Refer to ArrayRx.	Refer to coverage policies administered by ArrayRx.
Infliximab Products	Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620. Preferred: • Avsola (infliximab) • Inflectra (infliximab) Non-preferred: • Remicade (infliximab) • Other infliximab biosimilars (Ixifi, Renflexis) • Unbranded Janssen infliximab product

a. A diagnosis of **uveitis** is established by or in consultation with a specialist in ophthalmology.

AND

b. Treatment with corticosteroids (oral, periocular, or intravitreal injections) have been:

i. Ineffective after two weeks of therapy (for example, prednisone 40 to 60 mg/day).

OR

ii. Unable to be tapered following an adequate course without worsening of disease.

OR

iii. Not tolerated or is contraindicated.

AND

c. Treatment with at least one conventional agent was not effective after a 6-week treatment course, not tolerated, or all are contraindicated. Conventional agents for treatment of uveitis include azathioprine, cyclosporine, methotrexate, mycophenolate, or tacrolimus.

U. Other Immunologic Conditions: Pyoderma Gangrenosum, Sarcoidosis

1. For provider-administered therapies, site of care administration requirements must be met [refer to Medication Policy Manual, Site of Care Review, dru408].

2. Provider-administered therapies may be considered medically necessary when criteria a and b below are met.

3. For infliximab products: Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620.

FOR UMP MEMBERS:	
Preferred Self-Administered Options Refer to ArrayRx.	Refer to coverage policies administered by ArrayRx.
Non-Preferred Self-Administered Options Refer to ArrayRx.	Refer to coverage policies administered by ArrayRx.
Infliximab Products	Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620. Preferred: • Avsola (infliximab) • Inflectra (infliximab) Non-preferred: • Remicade (infliximab) • Other infliximab biosimilars (Ixifi, Renflexis) • Unbranded Janssen infliximab product

a. A diagnosis of **pyoderma gangrenosum** or **sarcoidosis** has been established by or in consultation with a specialist in pulmonology, rheumatology, immunology, or other specialist for the disease state.

AND

b. Treatment with a conventional immunomodulator (e.g., methotrexate, azathioprine, cyclosporine, hydroxychloroquine, leflunomide, or mycophenolate) was ineffective, or not tolerated. (See *Appendix 2* for additional conventional agents.)

IV. Administration, Quantity Limitations, and Authorization Periods

A. Pharmacy Services considers intravenously administered drugs in this policy coverable only under the medical benefit (as a provider-administered medication) (see *Table 1*).

B. Pharmacy Services considers Ilumya (tildrakizumab-asmn) coverable only under the medical benefit (as a provider-administered medication).

C. Pharmacy Services considers ustekinumab (Stelara; biosimilars Pyzchiva, Selarsdi, Wezlana) and Skyrizi (risankizumab) coverable under the pharmacy benefit (as self-administered medications) OR coverable under the medical benefit (as provider-administered medications).

D. Pharmacy Services considers the lyophilized powder formulation of Cimzia (certolizumab) coverable only under the medical benefit (as a provider-administered medication). Cimzia (certolizumab) prefilled syringes are coverable only under the pharmacy benefit (as a self-administered medication).

E. When pre-authorization is approved, each drug may be covered in the following quantities and for the following authorization periods outlined in *Table 1*.

TABLE 1. Authorization Limits

Product	Route	Authorization Limit
Cimzia (certolizumab)	SC (vial only)	**CD, RA, PsA, AS, NR-axSpA:** Up to 3 doses (six 200 mg vials) in the first month based on an initial dose of 400 mg SC at weeks 0, 2, and 4 followed by 200 mg every two weeks or 400 mg every four weeks for maintenance. (27 doses in the first 12-month period followed by up to 26 doses per 12-month period, thereafter). **PsO:** - Up to 400 mg (two 200 mg vials) every other week (up to 26 doses per 12-month period). - Authorization **may** be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective. Note: Certolizumab is available in pre-filled syringes and as a lyophilized powder vial (for SC injection). Both forms are given subcutaneously; however only the vials are considered provider-administered.
Cosentyx (secukinumab)	IV	**AS, NR-axSpA, and PsA:** Up to 13 infusions (with loading dose: 6 mg/kg at week 0, followed by 1.75 mg/kg every 4 weeks thereafter; without loading dose: 1.75 mg/kg every 4 weeks; both dosing regimens with a maximum maintenance dose 300 mg per infusion).
Entyvio (vedolizumab)	IV	**CD and UC:** - Initial authorization: Up to 6 doses (six 300 mg infusions) in a 6-month period based on a recommended starting interval of 300 mg infusions at zero, two and six weeks, then every eight weeks thereafter (9 infusions in the first 12-month period followed by up to 7 infusions per 12-month period, thereafter). - Dose escalation: A dosing interval of every 4 weeks (up to 13 infusions per 12-month period) may be considered medically necessary in patients who have had an inadequate response to every 8-week dosing given for at least 24 weeks. Dosing more frequent than every 4 weeks is considered investigational (see Table 4 *Investigational Uses: Dosing or Dose Escalation* for more information). Authorization **may** be reviewed at least annually and clinical documentation indicating that there is disease stability or improvement must be provided.
	IV	**Immune-Mediated Colitis:** Up to 6 doses (six 300 mg infusions) in a 6-month period based on a recommended starting interval of 300 mg infusions at zero, two and six weeks, then every eight weeks thereafter. Authorization **may** be reviewed at least annually and clinical documentation indicating that there is disease stability or improvement must be provided.

Product	Route	Authorization Limit
Ilumya (tildrakizumab -asmn)	SC	**PsO:** Up to two doses (two 100 mg syringes) in the initial four-week period followed by one dose (one 100 mg syringes) every 12 weeks thereafter based on an initial dose of 100 mg at weeks 0 and 4 followed by maintenance dosing of 100 mg every 12 weeks (up to five 100 mg syringes in the first 12-month period followed by four 100 mg syringes per 12-month period thereafter). Authorization **may** be reviewed at least annually to confirm that current medical necessity criteria are met, and that the medication is effective.
Omvoh (mirikizumab)	IV induction	**UC:** Up to 3 doses (three 300 mg infusions) in the first 8-week period based on a recommended starting interval of 300 mg infusions at 0, 4, and 8 weeks.
Orencia (abatacept)	IV	**aGVHD:** Up to 4 infusions (up to 10 mg/kg) in a 4-week period based on a dose of 10 mg/kg/ dose given on days −1, +5, +14, and +28 post-transplant. **RA, PJIA PsA:** Up to 3 infusions (up to 1000 mg) in the first 4-week period, based on weight-based loading doses at weeks 0, 2 and 4, followed by maintenance dosing of up to 13 infusions in a 12-month period, based on a dose of one infusion (up to 1000 mg) every 4 weeks (14 infusions in the first 12-month period followed by up to 13 infusions per 12-month period, thereafter). **RA:** A single IV loading dose (up to 1000 mg) may be authorized, if required prior to administration of self-administered Orencia SC. Authorization **may** be reviewed at least annually, and clinical documentation indicating that there is disease stability or improvement must be provided.
Simponi Aria (golimumab)	IV	**AS, PsA, RA:** Up to 2 infusions (up to 2 mg/kg) in the first 4-week period, based on weight-based loading doses at weeks 0 and 4, followed by maintenance dosing of up to 7 infusions in a 12-month period, based on a dose of one infusion (up to 2 mg/kg) every 8 weeks (8 infusions in the first 12-month period followed by up to 7 infusions per 12-month period, thereafter). **PJIA:** Up to 2 infusions (up to 80 mg/m^2) in the first 4-week period, based on body-surface-area-based loading doses at weeks 0 and 4, followed by maintenance dosing of up to 7 infusions in a 12-month period, based on a dose of one infusion (up to 80 mg/m^2) every 8 weeks (8 infusions in the first 12-month period followed by up to 7 infusions per 12-month period, thereafter). <u>Dose escalation:</u> Dosing interval of up to every 6 weeks may be considered medically necessary in patients who have had an inadequate response to every 8-week dosing given for at least 24 weeks. Authorization **may** be reviewed at least annually to confirm that current medical necessity criteria are met, and the medication is effective. Authorization **may** be reviewed at least annually, and clinical documentation indicating that there is disease stability or improvement must be provided.

<table>
<tr><th>Product</th><th>Route</th><th>Authorization Limit</th></tr>
<tr><td rowspan="2">Spevigo (spesolimab)</td><td>IV</td><td>GPP flare: Up to two 900 mg infusions given within a 4-week approval period, based on a single dose of 900 mg. A second additional 900 mg dose, given one week after the initial dose, may be given once if symptoms persist, within the 4-week approval period. NOTE: no more than two doses are coverable for any one flare.

For consideration of treatment of a <u>new flare</u> (after at least 4 weeks): Authorization shall be reviewed to confirm that current medical necessity criteria are met, including flare criteria, and that the medication was effective for the previously treated flare. Each additional flare authorization is for a maximum of two 900 mg doses over a 4-week approval period.</td></tr>
<tr><td>SC</td><td>GPP maintenance when <u>not</u> experiencing a flare (loading dose only): A single SC loading dose (600 mg dose) may be authorized, if required prior to administration of self-administered Spevigo SC.</td></tr>
<tr><td rowspan="2">Ustekinumab (Stelara; biosimilars Pyzchiva, Selarsdi, Wezlana)</td><td>SC (PsO and PsA)</td><td>PsO and PsA:
- For all patients, regardless of weight, up to five doses (five 45 mg syringes or vials) in a 48-week period based on dosing of 45 mg at week 0 and 4, then 45 mg every 12 weeks thereafter (up to five 45 mg syringes or vials in the first 12-month period followed by four 45 mg syringes or vials per 12-month period thereafter).
- <u>Dose escalation</u>: For patients in whom the 45 mg dose has shown benefit, but who have not achieved clinical remission after at least a 12-week trial, doses of up to 90 mg every 12 weeks may be considered medically necessary. Dosing more frequent than 90 mg every 12 weeks is considered investigational (see <u>Table 4 Investigational Uses: Dosing or Dose Escalation for more information</u>).

Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met, and the medication is effective.</td></tr>
<tr><td>IV Induction (CD and UC Only)</td><td>CD and UC Only: Initial: A single, weight-based IV infusion initially (vials, see chart below for details), then up to 6 doses (six 90 mg syringes or twelve 45 mg vials) based on maintenance dosing of 90 mg SC every 8 weeks. Initial IV dosing is as follows:
<table>
<tr><th>Weight</th><th>Dose</th></tr>
<tr><td>55 kg or less</td><td>260 mg (2 x 130 mg vial)</td></tr>
<tr><td>More than 55 kg to 85 kg</td><td>390 mg (3 x 130 mg vial)</td></tr>
<tr><td>More than 85 kg</td><td>520 mg (4 x 130 mg vial)</td></tr>
</table>
<u>Additional IV induction courses</u> doses may be considered medically necessary in patients who have previously had an inadequate response to every 8-week dosing given for at least 24 weeks or who have had a break in therapy.</td></tr>
</table>

Product	Route	Authorization Limit
	SC Maintenance dosing for CD and UC	**CD:** - Up to 7 doses (seven 90 mg syringes or fourteen 45 mg vials) in a one-year based on maintenance dosing of 90 mg SC every 8 weeks. - Dose escalation/Re-induction: A dosing interval of up to every 4 weeks be or additional IV doses may be considered medically necessary in patients who have had an inadequate response to every 8-week dosing given for at least 24 weeks. Authorization **may** be reviewed at least annually to confirm that current medical necessity criteria are met, and the medication is effective.
Skyrizi (risankizumab)	SC (PsA, PsO)	**PsA, PsO:** Up to 2 doses (four 75 mg syringes or two 150 mg syringes) in the initial four-week period followed by 150 mg (two 75 mg syringes or one 150 mg syringe) every 12 weeks based on dosing of 150 mg SC at weeks 0 and 4 followed by maintenance dosing of 150 mg every 12 weeks (up to twelve 75 mg syringes or six 150 mg syringes in the first 12-month period followed by up to ten 75 mg syringes or five 150 mg syringes per 12-month period, thereafter). Authorization **may** be reviewed at least annually to confirm that current medical necessity criteria are met, and the medication is effective.
	IV Induction (CD, UC)	**CD:** Up to 3 doses (three 600 mg infusions) in the first-8-week period based on a recommended starting interval of 600 mg infusions at zero, four, and 8 weeks, then up to 6 (six 180 mg or 360 mg cartridges) in the first 12-month period based on a maintenance dose of 180 mg or 360 mg given at week 12 and every 8 weeks thereafter. **UC:** Up to 3 doses (1,200 mg infusions) in the first 8-week period based on a recommended starting interval of 1200 mg infusions at zero, four, and 8 weeks, then up to 6 (six 180 mg or 360 mg cartridges) in the first 12-month period based on a maintenance dose of 180 mg or 360 mg given at week 12 and every 8 weeks thereafter).
	SC Maintenance dosing (CD, UC)	**CD, UC:** Up to 7 doses (seven 180 mg or 360 mg cartridges) per 12- month period based on maintenance dosing of 180 mg or 360 mg SC every 8 weeks. Authorization **may** be reviewed at least annually to confirm that current medical necessity criteria are met, and the medication is effective.

Product	Route	Authorization Limit
Tocilizumab (Actemra; biosimilars: Tofidence, Tyenne)	IV	**AMR:** Up to 7 infusions (up to 8 mg/kg with an 800 mg per infusion maximum) in a 6-month period based on a recommended infusion interval of every 4 weeks. Authorization **shall** be reviewed at least every 6 months to confirm that current medical necessity criteria are met, and the medication is effective. **RA and Takayasu Arteritis:** Up to 13 infusions (up to 8 mg/kg) in a 12-month period based on a recommended infusion interval of every 4 weeks. **PJIA:** Up to 13 infusions (up to 10 mg/kg) in a 12-month period based on a recommended infusion interval of every 4 weeks. **GCA:** Up to 13 infusions (up to 6 mg/kg) in a 12-month period based on a recommended infusion interval of every 4 weeks. **SJIA:** Up to 26 infusions (up to 12 mg/kg) in a 12-month period based on a recommended infusion interval of every 2 weeks. **CRS:** Up to 4 infusions (up to 12 mg/kg). No additional doses will be authorized. **For GCA, RA, PJIA, SJIA, and Takayasu Arteritis:** Authorization **may** be reviewed at least annually, and clinical documentation indicating that there is disease stability or improvement must be provided.
Tremfya (guselkumab)	IV Induction	**UC:** Up to 3 doses (200mg infusions) within an 8- week period based on a recommended starting interval of 200mg at week 0, 4, and 8. Induction to be followed by the recommended SC maintenance doses up to FDA-recommended dose, duration, and frequency limits described in its prescribing information.

aGVHD: Acute graft versus host disease; AMR: Antibody mediated rejection; AS: Ankylosing spondyloarthritis, CD: Crohn's disease, CRS: Cytokine release syndrome, ERA: Enthesitis-related arthritis; GCA: Giant cell arteritis; PJIA: Polyarticular juvenile idiopathic arthritis, NR-axSpA: Non-radiographic axial spondyloarthritis, PsA: Psoriatic arthritis, PsO: Plaque psoriasis, RA: Rheumatoid arthritis, SJIA: Systemic juvenile idiopathic arthritis; SpA: Spondyloarthritis, UC: Ulcerative colitis

V. Not Medically Necessary Uses

A. Therapies included in this policy are considered not medically necessary when used according to Table 2.

TABLE 2.

Ilumya (tildrakizumab-asmn) – Doses higher than 100 mg every 12 weeks	Doses > 100 mg every 12 weeks	- Ilumya (tildrakizumab-asmn) is considered not medically necessary when used in doses exceeding 100 mg every 12 weeks. - Ilumya (tildrakizumab-asmn) is FDA approved for PsO at a dose of 100 mg subcutaneously every 12 weeks. While clinical trials of Ilumya (tildrakizumab-asmn) in PsO evaluated doses 100 mg and 200 mg subcutaneously every 12 weeks, both doses appeared to have similar efficacy. Therefore, the use of doses higher than 100 mg every 12 weeks is considered not medically necessary. [1]
Ustekinumab (Stelara; biosimilars Pyzchiva), Selarsdi, Wezlana)	Initial doses of 90 mg for PsO/PsA	- Usteinkinumab (Stelara; biosimilars Pyzchiva, Selarsdi, Wezlana) is considered not medically necessary at initial doses of 90 mg per every 12 weeks regardless of weight. Given that more than half of all patients respond to the 45 mg dose and given the significant cost difference between the 45 mg and 90 mg doses, a trial of 45 mg for all patients regardless of weight represents the best treatment value. - Note: For patients in whom the 45 mg dose has shown benefit, but who have not achieved clinical remission after at least a 12-week trial, doses of up to 90 mg every 12 weeks may be considered medically necessary. - Dosing for ustekinumab was established through a post-hoc analysis of the results of the Phoenix 1 and Phoenix 2 trials. The recommended weight-based dosing scheme was not studied in a prospective manner. [2 3] Patients greater than 100 kg were found to have on average, a better response to treatment when receiving a dose of 90 mg every 12 weeks compared with 45 mg every 12 weeks. * In Phoenix 1, 68.5% and 54.0% of patients greater than 100 kg achieved PASI75 in the 90 mg and 45 mg groups, respectively. * In Phoenix 2, 71.1% and 49.1% of patients greater than 100 kg achieved PASI75 in the 90 mg and 45 mg groups, respectively. * When treatment with 45 mg has resulted in some benefit, but has not achieved clinical remission, a continuation of treatment with 90 mg may be appropriate. - There is no evidence to support the need for re-induction when the dose is escalated from 45 mg to 90 mg is made.

VI. Investigational uses

A. Combination use of targeted DMARDs, such as Otezla (apremilast) and tofacitinib (Xeljanz/Xeljanz XR), is considered investigational.

B. Unless otherwise specified in section I, therapies included in this policy are considered investigational when used for all other conditions, due to lack of published data, lack of high-quality data, or lack of positive data Details of select investigational uses are listed below in tables 3 and 4.

C. Unless specified in Section II (Administration, Quantity Limitations, and Authorization Periods) or Section III (Not Medically Necessary Uses), all dose escalations above the quantity limit are considered investigational (Additional details are in Table 4).

Table 3: Investigational Uses: Indications

Atopic Dermatitis	- Baricitinib is currently being evaluated for the treatment of atopic dermatitis. One preliminary, phase 2 study demonstrated that baricitinib may improve skin clearance compared to placebo. [4] However, longer-term, larger phase 3 studies are needed to confirm the benefit, identify the ideal population, and determine the appropriate dose.
Extraintestinal complications of IBD: Arthritis	- Arthritis is a common extraintestinal complication of IBD (either UC or CD). However, there is no reliable evidence to establish the efficacy or safety of targeted DMARDs in patients with arthritis associated with IBD who do not otherwise require targeted therapy. - The evidence is limited to small, short-term, open-label trials and case studies with infliximab. Given the lack of blinding and lack of control arm, the incremental benefit of infliximab therapy is uncertain. [5] - There are no reliable published clinical trials with any other biologic DMARDs for treatment of arthritis associated with IBD (in the absence of active bowel disease). - Of note: patients with IBD and a confirmed diagnosis of CD or UC with active bowel disease may be covered per Section I for management of IBD symptoms (active bowel disease). However, the isolated arthritis symptoms (in the absence of active bowel disease) is not coverable.
Blau's Syndrome (Familial Juvenile Systemic Granulomatosis)	- There is no reliable evidence to establish the efficacy or safety of targeted DMARDs in the treatment of Blau's syndrome. - No randomized, controlled trials have been published evaluating the use of adalimumab in patients with Blau's syndrome.
Graft Versus Host Disease (GVHD)	- There is no reliable evidence to establish the efficacy or safety of targeted DMARDs in the *treatment* of GVHD. - In one open-label clinical trial (n=62) incidences of GVHD-related mortality, non-relapse mortality, and overall survival were not different between patients treated with infliximab or placebo. [6]

Granuloma Annulare	- There is no reliable evidence to establish the efficacy or safety of targeted DMARDs in the treatment of granuloma annulare. - While case reports have been published describing the treatment of granuloma annulare with etanercept, other reports have been published describing no effect, or an association with the formation of granuloma annulare and treatment with TNF-alfa inhibitors, including etanercept. Additional information is necessary to the benefit of etanercept in this population. [7]
Guttate Psoriasis	- Guttate psoriasis is a type of cutaneous psoriasis. It is characterized by the presence of small, erythematous papules whereas plaque psoriasis is characterized itchy, red, scaly, raised lesions on the skin. Guttate psoriasis is typically managed with topical agents or UV light therapy. - There is no evidence to establish the efficacy or safety of targeted DMARDs in the treatment of guttate psoriasis.
Immune-mediated reactions (other than colitis or CRS with CAR-T cell therapy) due to immunotherapy	- There is no reliable evidence to establish the efficacy of safety of targeted DMARDs in the treatment of immune-mediated reactions, including but not limited to pneumonitis, hepatitis, or arthritis, due to PD-1, PDL-1, or CTLA4 inhibitors. - PD-1, PDL-1, and CTLA4 inhibitors contain warnings for immune-mediated hepatitis. In clinical trials, patients who experienced immune-mediated hepatitis were managed with systemic corticosteroids and mycophenolate. - For immune-mediated hepatitis, NCCN guidelines state that mycophenolate is recommended instead of infliximab due to the concern for hepatotoxicity with infliximab.
Reactive Arthritis/Reiter's Syndrome	- There is no reliable evidence to establish the efficacy or safety of targeted DMARDs in the treatment of reactive arthritis/Reiter's Syndrome.

Sciatica	- There is no reliable evidence to establish the efficacy or safety of targeted DMARDs in the treatment of sciatica. - Evidence for infliximab in the treatment of sciatica is limited to a randomized controlled trial in 40 patients. At 52 weeks, 67% of patients who received infliximab reported no pain compared with 63% of patients who received placebo (p = 0.72). This difference was not statistically significant. [8 9] - There are no randomized controlled trials that evaluate the efficacy and safety of a commercially available formulation of etanercept in the treatment of sciatica. - Evidence for adalimumab in the treatment of sciatica in limited to a small randomized, controlled trial evaluated adalimumab in 61 patients. There was a modest improvement in pain as measured by a 10-point visual analog scale and at three years, the need for back surgery was reduced in adalimumab-treated patients; however, larger clinical trials are needed to confirm the benefit of adalimumab in this population. [10 11]
Scleroderma	- There is insufficient evidence to support the use of tocilizumab for scleroderma. The evidence is limited to one small, placebo-controlled, phase 2 trial using subcutaneous tocilizumab (n=88). The trial found a change in modified Rodan skin score, but no significant difference in skin thickening, disability, fatigue, itching, or patient or clinician global disease severity. Larger Phase 3 trials are needed to establish the safety and efficacy of tocilizumab for scleroderma. [12]
Sjögren's Syndrome	- There is no reliable evidence to establish the efficacy or safety of targeted DMARDs in the treatment of Sjögren's syndrome. - Evidence for etanercept in Sjögren's syndrome is limited a small trial, in which there were no significant differences in the subjective measures of disease severity. [13] - Evidence for anakinra is limited to a placebo-controlled trial in which patients with Sjögren's syndrome failed to find a statistically-significant improvement in fatigue as measured by a visual analog scale in patient receiving anakinra compared with placebo. An ad-hoc analysis found suggestions of a clinically relevant effect, but larger, well-designed trials are needed to establish safety and efficacy for Sjögren's syndrome. [14]

Systemic Lupus Erythematous (SLE)	- There is no reliable evidence to establish the efficacy or safety of targeted DMARDs in the treatment of SLE. - A small uncontrolled clinical trial reported modest efficacy with infliximab in patients with systemic lupus erythematosus, though larger, better designed trials are needed to confirm these results. [15] - A small preliminary study assessing the use of tocilizumab in patients with SLE found promising signs of response, but larger, controlled studies will be needed to establish the efficacy and safety in this population. [16] - One small randomized, placebo-controlled trial evaluated the use of abatacept in patients with non–life-threatening SLE and polyarthritis. The primary endpoint (proportion of patients with a new flare of SLE) was not met but was suggestive of a positive effect in certain exploratory measures. Further study is needed to establish the safety and efficacy of abatacept in SLE. [17] - One 24-week, phase 2 study evaluated the use of baricitinib in patients with SLE. Results demonstrated that baricitinib 4 mg once may reduce SLE disease activity; however, results for the 2 mg dose were not significant. Larger, longer-term studies are needed to clarify the benefit of baricitinib in SLE. [18]
Wegener's Granulomatosis	- There is no reliable evidence to establish the efficacy or safety of targeted DMARDs in the treatment of Wegener's Granulomatosis. - Evidence for infliximab is limited to one small clinical trial in 17 patients. Both infliximab and rituximab appeared to provide benefit in achieving complete or partial response; however, there was a trend favoring rituximab. Additionally, rituximab was better able to maintain remission during the long-term follow-up. [19]

Table 4: Investigational Uses: Dosing or Dose Escalation

Combination use of targeted immunomodulators	- The use of combination (more than one) targeted DMARD therapy, such as Humira (adalimumab), Otezla (apremilast), tofacitinib (Xeljanz/Xeljanz XR), or Entyvio (vedolizumab), is considered investigational (includes all medications included in this policy; see table 5 for a complete list of targeted DMARDs). *Combination use of apremilast and other targeted immunomodulators* - There is no reliable evidence to establish the efficacy or safety of the combined use of apremilast and other targeted DMARDs (such as biologics) in the treatment of PsO or PsA. - There are no randomized, controlled trials evaluating the combined use of apremilast and any other targeted DMARD. The evidence is limited to retrospective studies in small numbers of patients. Additional studies are needed to establish long-term efficacy and the overall risk-benefit profile of combination use.
Secukinumab – Maintenance doses higher than 300 mg every 4 weeks for PsA or PsO	- There is insufficient evidence to support the use of secukinumab at maintenance doses higher than 300 mg every 4 weeks for PsO. - Phase 3 clinical trials of secukinumab for PsA and PsO evaluated maintenance dosing regimens of 150 mg or 300 mg every 4 weeks. Higher or more frequent doses have not been evaluated. It is uncertain if there is any additional benefit with increased dosing and the safety profile has not been evaluated.
Ustekinumab – Doses higher than 90 mg every 12 weeks for PsO or PsA	- There is insufficient evidence to support the use of ustekinumab at maintenance doses higher than 90 mg every 12 weeks for PsO or PsA. - There are no randomized, controlled trials to support doses higher than 90 mg every 12 weeks in PsO or PsA.
Vedolizumab - Doses higher than 300 mg every 4 weeks	- There is insufficient evidence to support the use of vedolizumab at maintenance doses higher than 300 mg every 4 weeks for CD and UC. - In phase 3 clinical studies of vedolizumab in CD and UC the highest dose of vedolizumab used was 300 mg every four weeks. Higher or more frequent doses have not been evaluated.

Position Statement

- ArrayRx's preferred self-administered products can be found at: https://www.hca.wa.gov/assets/pebb/ump-preferred-drug-list-2024.pdf.
- There are many treatments for chronic inflammatory conditions that are effective, have known long-term safety profiles, and are recommended by national treatment guidelines.
- The intent of this policy is to allow coverage of each medication in settings where it has been safe and effective, with coverage after use of lower cost standard of care therapies, including preferred targeted DMARD options.
- Non-medical therapies, such as prescribed exercise therapy, physical therapy, weight loss, and smoking cessation are important treatment plan components for patients suffering from many chronic inflammatory conditions.
- When a systemic medication therapy is needed to manage a chronic inflammatory condition, generic oral therapies usually offer the best value.
- When non-medical therapies and oral medications are inadequate, a targeted DMARD or immunomodulator [conventional synthetic DMARD (csDMARD)] may be appropriate and use is supported by guidelines. Targeted DMARDs, include non-biologics and biologics. Biologics include both anti-TNF and non-anti-TNF options.
- When there is no demonstrated difference in safety or efficacy among the studied targeted DMARDs, the medication with the lowest cost often provides the best value for members.
- Individual responses and tolerability of targeted DMARDs, including biologics, are unpredictable and may vary between patients. If one targeted DMARD provides an inadequate response, another targeted DMARD may yet be effective.
- Due to the potential for development of antibodies with anti-TNF therapies which may result in loss of efficacy, clinical practice guidelines generally recommend a trial with one to two anti-TNF therapies. [20-24] For those who have an inadequate response or intolerance to a TNF inhibitor, it is reasonable to consider a targeted treatment with an alternative mechanism of action and proven efficacy for the patient's diagnosis.
- All DMARDs, conventional and targeted, are immunosuppressants and carry a risk of increased infection. Risk and infection type varies by mechanism of action and medication.
- 2021 JAK inhibitors label updates placed their usage after other systemic therapies for the indications in which they have FDA approval due to safety concerns (which include major cardiovascular events and mortality among other concerns).
- There is significant variation in recommended dosing across indications for individual medications, particularly with targeted agents; therefore, when multiple dosage forms of a targeted agent are available, coverage can be provided for those indications where the dosage form has been evaluated in randomized controlled trials, the dosage form has been proven safe and effective, and for which the dosage form has an established dose. For all other indications, the specific dosage form will be considered investigational.
- Inflectra (infliximab-dyyb) and Avsola (infliximab-axxq) are the preferred infliximab

products. The reference products and other biosimilars such as Renflexis (infliximab-abda) and Ixifi (infliximab-qbtx) are considered non-preferred. While they share most indications with each other, they are not the preferred formulation of infliximab.

- The medications in this policy, including loading doses, are coverable for the lowest effective doses, aligned with how they were studied in clinical trials, including use of loading doses.

Evidence summary:

Rheumatic Conditions – Background

- Treatments for rheumatic conditions may include non-medical therapies, medications for the management of symptoms, medications that modify the disease course such as conventional synthetic or targeted disease modifying anti-rheumatic drugs (DMARDs).
- Medications to control inflammation such as nonsteroidal anti-inflammatory medications (NSAIDs, e.g., ibuprofen, indomethacin, and naproxen) and glucocorticoids (oral or injected into the joint) are effective for the management of symptoms, particularly during the early stages of disease.
- Generic, conventional synthetic DMARDs (csDMARDs), including MTX (methotrexate), hydroxychloroquine, leflunomide, and sulfasalazine are effective for decreasing symptoms and slowing disease progression, and are recommended by current guidelines.
    * MTX is generally the initial csDMARD for rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA).
    * csDMARDs have known risks. The management of these risks is well established.
- Targeted DMARDs can also decrease symptoms, help preserve joint functioning, and slow the progression of the disease.
- In JIA, combination therapy with a csDMARD is strongly recommended for infliximab to reduce the risk of anti-drug antibodies against infliximab. [25]

Rheumatic Conditions – Enthesitis-related Arthritis (ERA)

- ERA is a type of juvenile idiopathic arthritis (JIA) that causes swelling or inflammation of the entheses (tendon-to-bone insertion sites).
- 2019 ACR guidelines for JIA recommend NSAIDs as initial therapy for patients with ERA followed by TNF inhibitors. Methotrexate or sulfasalazine may be used if TNF inhibitors are contraindicated. ACR guidelines have not been updated to include secukinumab. [26]
- There is little comparative evidence to distinguish among the biologic options for ERA due to the lack of head-to-head comparisons.
- The evidence for secukinumab in ERA is based on one small placebo-controlled phase III withdrawal trial that demonstrated a reduced time to disease flare for those on secukinumab versus placebo. [27]

Rheumatic Conditions – Axial Spondyloarthritis (SpA)

- Axial spondylarthritis (SpA) is a form of inflammatory arthritis that includes ankylosing spondylitis (AS) and non-radiographic axial spondylarthritis (nr-axSpA).

- Several targeted DMARDs have been shown to be effective in the treatment of AS or nr-axSpA.
- There is moderate quality evidence to support the use of targeted DMARDs, particularly TNF inhibitors, in non-radiographic axial SpA. Clinical trials have consistently shown that treatment with TNF inhibitors reduced disease activity in this population.
- 2019 ACR guidelines do not recommended any one TNF inhibitor over another except in patients who also have inflammatory bowel disease or iritis in which case adalimumab or infliximab would be recommended over etanercept. Cosentyx (secukinumab) and Taltz (ixekizumab) are recommended as second-line options in patients who have active symptoms without response to a previous TNF inhibitor. TNF inhibitors, secukinumab, or ixekizumab are recommended over tofacitinib in patients with AS. [28]
- Because of similar efficacy among the studied targeted DMARDs, non-preferred/non-formulary options are coverable when preferred/formulary options are ineffective, as detailed in the coverage criteria in Section I.

Rheumatic Conditions – Polyarticular Juvenile Idiopathic Arthritis (PJIA); Juvenile Rheumatoid Arthritis (JRA)

- Several targeted DMARDs (as listed in the coverage criteria) have been shown to be effective in the treatment of JIA.
- 2019 ACR guidelines for JIA recommend methotrexate, leflunomide, or sulfasalazine as initial therapy for patients with JIA. Methotrexate is recommended over leflunomide and sulfasalazine due to a larger body of evidence. Biologic agents are recommended in patients who have disease activity despite treatment with methotrexate, sulfasalazine, or leflunomide or in patients with high disease activity or have disease in high-risk joints. [25]
- Combination therapy with a biologic and a csDMARD is recommended to prevent the formation of anti-drug antibodies.
- There is little comparative evidence to distinguish among the targeted options for JIA. Guidelines state that there are mostly equivalent data for safety and efficacy between the biologics and there are lack of head-to-head comparisons between them.
- In patients who have had an inadequate response to a TNF inhibitor, switching to a non-TNF biologic is preferred over a second TNF inhibitor. However, a second TNF inhibitor may be appropriate if patients had a good response to the initial TNF inhibitor. [25]

Rheumatic Conditions – Psoriatic Arthritis (PsA)

- Several targeted DMARDs (as listed in the coverage criteria) have been shown to be effective in the treatment of PsA.
- ACR Guidelines recommend TNF inhibitors as the first-line treatment for PsA. However, other mechanisms can be used in patients with contraindications to TNF inhibitors. The guidelines do not specify the use of any one TNF inhibitor over another. [29]
- In patients who have failed a TNF inhibitor, a second TNF inhibitor is recommend over switching to a different mechanism of action (e.g., an IL-12/23 inhibitor, biologic, IL-17 inhibitors, abatacept, or tofacitinib). However, a different mechanism of action may be

used in cases of primary TNF inhibitor failure (no response) or a serious adverse event due to a TNF inhibitor. [29]

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- Because of similar efficacy among the studied targeted DMARDs, non-preferred/non-formulary options are coverable when preferred/formulary options are ineffective, as detailed in the coverage criteria.

Rheumatic Conditions – Rheumatoid Arthritis (RA)

- Several targeted DMARDs (as listed in the coverage criteria, as well as rituximab) have been shown to be effective in the treatment of RA.
- The efficacy of these targeted DMARDs in the treatment of RA is similar. Guidelines do not recommend one specific targeted DMARD. The initial choice of therapy includes biologic DMARDs (TNF inhibitors or a non-TNF biologic) or targeted synthetic DMARDs (e.g., JAK inhibitors). However, 2021 ACR guidelines have not accounted for recent drug safety communications regarding the risk of serious heart-related events with JAK inhibitors. [30 31]
- In patients who have had an inadequate response to targeted therapy, guidelines recommend switching to a targeted DMARD of a different class rather a different DMARD of the same class. [30]
- Guidelines have recommendations for specific patient populations including non-TNF inhibitors over TNF inhibitors for patients with New York Heart Association (NYHA) class III or IV heart failure. This recommendation is based on the risk of worsening heart failure observed in RCTs of TNF inhibitors in patients with heart failure. [30]
- Because of similar efficacy among the studied targeted DMARDs, non-preferred/non-formulary options are coverable when preferred/formulary options are ineffective, as detailed in the coverage criteria.

Rheumatic Conditions – Systemic Juvenile Idiopathic Arthritis (SJIA)

- Several targeted agents (as listed in the coverage criteria) have been shown to be effective or are recommended by clinical practice guidelines in the treatment of SJIA. [21]
- Due to lack of high-quality data, the comparative efficacy for these agents in the treatment of SJIA is uncertain.
- The efficacy of these targeted DMARDs (as listed in the coverage criteria) in the treatment of SJIA is similar. However, there is a significant difference in the cost between these treatment options. Therefore, the costlier treatment options are coverable only when the less costly options are ineffective.

Rheumatic Conditions – Giant Cell Arteritis (GCA)

- Data evaluating the use of biologic agents in the treatment of GCA is limited; however, there are few treatment options for this condition, which can result in serious complications.
- Subcutaneous Actemra (tocilizumab) in combination with prednisone has been shown to improve remission rates compared prednisone alone in patients with *newly diagnosed or relapsing* GCA. [32]
- Intravenous Actemra (tocilizumab) is approved for the treatment of GCA; evidence is

based primarily on pharmacokinetic exposure data and extrapolation to the efficacy established for subcutaneous tocilizumab in patients with GCA. [33]

- Evidence for the use of TNF inhibitors is lacking, as several small trials have not shown benefit in the treatment of GCA.

Skin Conditions – Chronic Plaque Psoriasis (PsO)

- There are many treatments for chronic plaque psoriasis (PsO) that are effective, have known long-term safety profiles, and are recommended by national treatment guidelines.
- Light therapy, including UVB and PUVA, is effective and safe, and PUVA may result in long-term remission. When patients are not able to receive office-administered light therapy, light units for home use may be an appropriate alternative (see Appendix 1 for absolute and relative contraindications for phototherapy/photochemotherapy).
- AAD guidelines (2014) recommend phototherapy after failure of first-line treatment (emollients, topical steroids, and topical calcineurin inhibitors). Most patients with mild-to-moderate psoriasis can achieve adequate control with topical medications or phototherapy.
- When systemic therapy is needed to manage psoriasis, csDMARDs often provide the best value. [34]
    * Conventional synthetic DMARDS (csDMARDs), including MTX, cyclosporine, and Soriatane (acitretin), have a proven track record and have been the standard of care for many years.
    * csDMARDs typically take effect with 6 weeks though some patients may require 12 weeks to have full effect. Among these options, cyclosporine is known to work rapidly.
    * Like all immunosuppressants, including targeted DMARDs, the csDMARDs have known risks. The management of these risks is well established.
- Targeted DMARD may be appropriate for patients with moderate to severe psoriasis (e.g., at least 10% BSA and/or significant pain or functional impairment due to the PsO or when conventional topical or oral therapies, or phototherapy have been inadequate.
- Several targeted DMARDs (as listed in the coverage criteria) have been shown to be effective in the treatment of moderate to severe PsO.
- Within each drug class, efficacy of each drug is similar. In general, agents directed against IL-17 (i.e., secukinumab) or IL-23 (i.e., guselkumab) are more effective at producing skin clearance than TNF inhibitors and other mechanisms of action. [34] Because of similar efficacy within each class, non-preferred/non-formulary options are coverable when preferred/formulary options are ineffective, as detailed in the coverage criteria.

Skin conditions – Generalized Pustular Psoriasis [35-37]

- GPP is a rare subtype of psoriasis. Flares are characterized by an abrupt onset of widespread painful pustules which can coalesce into larger, “lakes of pus” overlying painful erythema. Significant flares are often accompanied by systemic symptoms,

notably fever, general malaise, and extracutaneous manifestations such as arthritis, uveitis, and neutrophilic cholangitis, and may be associated with life-threatening complications.

- Acute flares may be idiopathic or may be triggered by infection, withdrawal, or administration of certain medications (including those used in the treatment of GPP such as corticosteroids, methotrexate, or tumor necrosis factor [TNF] inhibitors), pregnancy, or stress.
- Treatment guidelines recommend the identification and management of potential triggers.
- Choice of therapy depends on disease acuity. Acitretin and methotrexate are the preferred initial treatments for adults with relatively stable GPP due to their relatively slow onset of action. They can be used for long-term maintenance treatment.
- Cyclosporine and infliximab are used for more severe, acute GPP. Cyclosporine or infliximab are often considered first line for severe GPP due to their rapid onset of action. Once control of acute disease is achieved, patients may be maintained on fast-acting therapies or transitioned to acitretin or methotrexate for long-term treatment. There is no comparative data regarding relative efficacies of agents used for GPP.

Skin Conditions – Hidradenitis Suppurativa

- High-quality data evaluating the use of targeted DMARDs in the treatment of hidradenitis suppurativa (HS) are limited; however, there are relatively few treatment options for this condition.
- Although adalimumab is FDA approved for the treatment of HS, infliximab also has data to support use in this indication. [38]
    * A high-quality systematic review showed that weekly-dosed adalimumab improved quality of life in HS compared to placebo; although, the effect size was approximately equal to what is considered a minimally clinically important difference.
    * In the same systematic review, infliximab also improved quality of life compared to placebo, with an effect size well above the threshold for a minimally clinically important difference.
- Trials of adalimumab in HS only included patients with more severe disease, defined as Hurley Stage II or III disease and with at least three abscesses or inflammatory nodules.
- Trials showed that adalimumab significantly improved the hidradenitis suppurativa response rate after 12 weeks of treatment; however, efficacy and safety beyond 12 weeks of treatment has not been established. [39 40]
- Additional long-term randomized controlled trials are needed to understand relative efficacy of other treatments, the safety associated with weekly-dosed adalimumab, and role of oral, non-biologic/non-targeted DMARD treatments for HS.
- Evidence-based guidelines for hidradenitis suppurativa are not available, primarily due to lack of data. However, standard of care therapy reviews suggest the following:
    * Patients may benefit from non-pharmacologic interventions such as good personal hygiene, smoking cessation, and weight-loss.
    * For mild to moderate HS, topical clindamycin and tetracyclines have a proven track record of safety and have been the standard of care.

* When systemic therapy is needed to manage refractory hidradenitis suppurativa, oral therapies often provide the best value. Options include systemic antibiotics (e.g., oral tetracyclines, clindamycin, rifampin, moxifloxacin, metronidazole), hormonal therapies (e.g., oral contraceptives, spironolactone), cyclosporine, finasteride, metformin, or oral retinoids.

Gastrointestinal conditions – Background

- There are many treatments for Crohn's disease (CD) and ulcerative colitis (UC) that are effective, have known long-term safety profiles, and are recommended by national treatment guidelines. [41]
- Lifestyle interventions, such as smoking cessation and diet modification, are important components of a comprehensive treatment plan for patients suffering from CD. [41]
- When medication therapy is needed to manage CD and UC, oral and topical (administered rectally) therapies often provide the best value. [41]
  * First-line therapies to induce remission include:
    - Patients with CD: oral corticosteroids, budesonide, aminosalicylates (e.g., sulfasalazine or mesalamine). [41]
    - Patients with UC: oral aminosalicylates (5ASAs, such as sulfasalazine), topical mesalamine or corticosteroids (e.g., budesonide), or oral corticosteroids, depending on the extent and location of disease.
    - Due to the potential for severe adverse effects, the use of conventional corticosteroids such as prednisone is generally reserved for patients with moderate-to-severe disease who failed to respond to first-line therapies. Use is generally limited to one to two weeks. [41]
    - Corticosteroids such as prednisone are effective in patients with both CD UC. Dosages in the range of 40 mg – 60 mg/day or 1 mg/kg/day of prednisone or equivalent are effective for induction of remission. [41]
  * Once maintenance is induced with corticosteroids, maintenance therapy with azathioprine, 6-mercaptopurine, or methotrexate should be initiated. Azathioprine, 6-mercaptopurine, or methotrexate are slow acting and can take 8 to 12 weeks to have full effect.
  * First-line therapies to maintain remission include:
    - Patients with CD: MTX, 6-mercaptopurine, and azathioprine.
    - Patients with UC: oral aminosalicylates (e.g., sulfasalazine), topical mesalamine or corticosteroids, or oral corticosteroids, depending on the extent and location of disease.
- When non-medical therapies and oral/topical therapies (steroids or csDMARDs) are inadequate, a targeted DMARD may be appropriate for induction and/or maintenance of disease remission.

Gastrointestinal conditions –Crohn's Disease (CD) and Ulcerative Colitis (UC)

- There are many treatments for Crohn's disease (CD) and ulcerative colitis (UC) that are effective, have known long-term safety profiles, and are recommended by national treatment guidelines. [41]

- Several targeted DMARDs (as listed in the coverage criteria) have been shown to be effective in the treatment of CD and/or UC, for inducing and maintaining remission compared to placebo.
- Due to a lack of head-to head comparative studies, the overall comparative efficacy for these targeted DMARDs in the treatment of CD is uncertain. There is also a lack of comparative evidence for treatment of UC. Therefore, non-preferred/non-formulary options are coverable when preferred/formulary options are ineffective, as detailed in the coverage criteria.
- Although studied in UC, there are no controlled trials of golimumab in CD. Likewise, although studied in CD, there are no controlled trials of certolizumab or natalizumab in UC.
- Restorative proctocolectomy with ileal pouch–anal anastomosis (IPAA) is routinely performed in patients with UC who undergo colectomy. Idiopathic inflammation of the pouch — referred to as pouchitis — is the most common long-term complication of IPAA. Retrospective, uncontrolled studies suggest that TNF antagonists, vedolizumab, or ustekinumab may be effective in the treatment of pouchitis that is refractory to antibiotics.[42]
- Safety considerations:
    * Due to an increased risk of mortality and thrombosis with tofacitinib 10 mg twice daily or tofacitinib 22 mg daily, tofacitinib is only indicated for patients who have previously had an inadequate response or intolerance to TNF inhibitors.
    * Use of tofacitinib 10 mg twice daily or tofacitinib 22 mg daily should be limited to the shortest duration, with consideration of the benefits and risks for the individual patient. The prescribing information states that the lowest effective dose needed to maintain response should be used.

Guidelines: [41] [44 45]

- Lifestyle interventions, such as smoking cessation and diet modification, are important components of a comprehensive treatment plan for patients suffering from CD.
- When medication therapy is needed to manage CD and UC, oral and topical (administered rectally) therapies often provide the best value.
- First-line therapies to induce remission for CD/UC vary, based on severity and anatomic distribution, but may include:
    * Oral corticosteroids, “topical” steroids (enteric-coated budesonide), oral aminosalicylates (5ASAs, such as sulfasalazine or mesalamine). Steroids are used over csDMARDs for induction of remission in moderate to severe UC. Several product formulations are specific to anatomic location of the disease, such as enteric-coated (EC) budesonide or EC mesalamine, or rectal 5ASAs.
    * In addition, topical mesalamine may be used for UC, depending on the extent and location of disease.
    * The use of conventional corticosteroids, such as prednisone, is generally reserved for patients with moderate-to-severe CD/UC refractory to first-line therapies, given the adverse events. Use is generally limited to one to two weeks.

    * Corticosteroids, such as prednisone, (40 - 60 mg/day or 1 mg/kg/day), are effective for induction of remission for CD and UC.

- Once maintenance is induced with corticosteroids, remission csDMARD therapy should be initiated. Choice of therapy varies between CD and UC, as well as response to induction therapy(s). Antimetabolite csDMARDs [such as MTX (methotrexate), 6-MP (6-mercaptopurine), azathioprine)] are slow acting and can take 8 to 12 weeks to have full effect. They are also used to decrease immunogenicity in combination with targeted DMARDs.
- First-line therapies to maintain remission include:
    * CD: 6-mercaptopurine, azathioprine, and methotrexate.
    * UC: oral 5ASAs (e.g., sulfasalazine), topical mesalamine or corticosteroids, or oral corticosteroids, depending on the extent and location of disease.
- When non-medical therapies and oral/topical medications (steroids or aminosalicylates) are inadequate, a targeted DMARD may be appropriate for induction and/or maintenance of disease remission.
- Guidelines for CD list multiple targeted DMARDs as effective treatment options. [41]
    * TNF inhibitors, including infliximab and adalimumab, are recommended in patients who are resistant to corticosteroids or whose disease is refractory to csDMARDs such as azathioprine or 6-mercaptopurine.
    * Ustekinumab is an option for moderate-to-severe CD patients who failed previous treatment with corticosteroids, thiopurines, methotrexate, or anti-TNF inhibitors or who have had no prior exposure to anti-TNF inhibitors.
    * Vedolizumab is also listed as an effective option for the induction and maintenance of remission in CD.
    * Due to the risk of progressive multifocal leukoencephalopathy (PML), a serious (sometimes fatal) adverse event, natalizumab is only recommended after other treatment options have failed.
    * Patients with fistulizing disease and severely active disease may be candidates for initial targeted DMARD. Definitions for severe disease include the following previous hospitalization for Crohn's disease, extensive anatomic involvement, deep ulcers, prior surgical resection, stricturing and/or penetrating behavior.
- Clinical practice guidelines for the treatment of UC indicate that for patients who initially respond to infliximab but lose response, an increase in dose or shortening of the interval between infusions may improve the likelihood of successful treatment. These guidelines acknowledge that these strategies have not been evaluated in a controlled manner.
- Lack of response and loss of response to TNF inhibitors is common in both CD and UC. The choice of subsequent agent after failure of a TNF inhibitor is typically guided by serum levels. ACG guidelines state that, in patients with adequate serum levels of anti-TNF antibodies switching to another TNF is unlikely to be of benefit.

Gastrointestinal conditions – Immune-mediated Colitis

- Serious or steroid-refractory colitis is a known adverse event associated with checkpoint

inhibitors such as Yervoy (ipilimumab), Opdivo (nivolumab), Keytruda (pembrolizumab), Tecentriq (atezolizumab), Bavencio (avelumab), Libtayo (cemiplimab), and Imfinzi (durvalumab). NCCN guidelines recommend prednisone or methylprednisolone as the first-line treatment for moderate colitis. Infliximab may be considered if there has been no improvement within 2-3 days of initiating glucocorticoids. [46]

- NCCN guidelines state that the duration of therapy with TNF-inhibitors is not clearly defined but is usually a single dose. [46]

Gastrointestinal conditions- collagenous colitis

- The European Guidelines on Microscopic Colitis (including lymphocytic colitis and collagenous colitis) recommend budesonide as front line for both induction as well as maintenance in some cases. Evidence for use of second-line therapies in patients with microscopic colitis is scarce and based primarily on case reports. Guidelines support the use of TNF inhibitors and vedolizumab for refractory microscopic colitis. TNF inhibitors, including infliximab and adalimumab, have been reported to induce remission. Vedolizumab has been associated with clinical remission based on case reports; almost all patients were refractory to prior TNF inhibitors; however, no randomized control trials have been published to date.[47]

Other Immunologic Conditions

Acute Graft Versus Host Disease (aGVHD)[48]

- Graft versus host disease (GVHD) is a common complication of allogeneic hematopoietic cell transplant (HCT) that occurs when the graft (donor) cells identify the transplant recipient cells (host) as foreign and initiates an immune reaction that may lead to organ damage or death.
- The risk for GVHD is higher when receiving a HCT from an unrelated donor.
- There are no standard guidelines for prophylaxis of acute GVHD, protocols vary by transplant center. The choice of therapy may depend on the underlying disease, degree of HLA disparity, conditioning regimen, and patient characteristics. Several regimens include a calcineurin inhibitors (tacrolimus, cyclosporine) given with either methotrexate or mycophenolate mofetil. Post-transplantation with cyclophosphamide or T-cell depletion is also used.
- At 6 months post-transplant, abatacept was shown to increase acute GVHD free survival as well as improve overall survival when used for patients with 8/8 HLA matched or 7/8 HLA mismatched unrelated donor HCT when used in combination with a calcineurin inhibitor plus methotrexate. [49]

Antibody Mediated Rejection of Transplant (solid-organ)[50 51]

- Acute allograft (organ) rejection may be cellular (T-cell mediated) or humoral (antibody-mediated) (AHR, AMR).
- Pre-treatment (desensitization) may reduce the risk of AMR in highly sensitized renal transplant patients.
- Acute humoral rejection (AHR) is also an AMR and can occur outside of the peri-operative period, but most commonly within 6 months after transplant. The diagnosis is confirmed by a renal biopsy.

- The goal of therapy is early antibody elimination with IVIG, pheresis, or a combination of modalities. However, evidence for therapies used in AMR are generally of low quality and protocols vary between transplant centers. PLEX and IVIG are generally regarded as a standard of care for acute active AMR. Rituximab has also been suggested as a treatment option by KDIGO guidelines. [50]
- One study assessed the use of tocilizumab as rescue therapy in 36 kidney transplant patients with chronic AMR who failed standard-of-care treatment with IVIG and rituximab, with or without plasma exchange. Tocilizumab was administered as 8 mg/kg monthly, with a maximal dose of 800 mg for 6 to 25 months. Graft- and patient- survival rates were 80% and 91% at six years post treatment, respectively.
- In a small pilot study (N=10), patients who did not respond to desensitization with IVIG and rituximab (+/- plasma exchange) who were given tocilizumab 8 mg/kg on day 15 then monthly for 6 months with IVIG had a decrease in donor specific antibodies. [52]

Pyoderma Gangrenosum

- Pyoderma gangrenosum (PG) is a rare ulcerative skin condition that is often associated with underlying systemic disease. First-line options for PG typically are systemic corticosteroids, cyclosporine, or tacrolimus. Infliximab is considered a second-line option when there has been an inadequate response. Infliximab or other biologic therapy may use when there is an underlying inflammatory condition, such as ulcerative colitis. [53 54]

Sarcoidosis

- Sarcoidosis is a multisystem granulomatous disorder characterized by the presence of granulomas in involved organs. It most commonly impacts the lungs and lymph nodes but may manifest in other organs. [55]
- Corticosteroid therapy is the primary therapy. Second line agents are considered for patients with corticosteroid-refractory disease. Second-line options include csDMARDs such as azathioprine, methotrexate, and leflunomide. Biologic therapy with infliximab is reserved for patients who have not responded to prior conventional agents. [55 56]

Takayasu arteritis

- Takayasu arteritis is a rare type of vasculitis where inflammation damages the aorta. Takayasu arteritis is complex and requires specialist management to accurately diagnosis and manage the condition. High dose corticosteroids in combination with csDMARDs are recommend as the initial treatment options. Tocilizumab and infliximab are recommended as second line options in patients who are unable to taper off oral corticosteroids or who have a relapse despite treatment with corticosteroids in combination with a csDMARD. [57]
- Actemra (tocilizumab) has been evaluated at doses of 8 mg/kg intravenously every 4 weeks or 162 mg subcutaneously weekly. There is limited information on the efficacy of higher doses. [57-60]

Uveitis

- Corticosteroids are the mainstay of therapy in uveitis. Guidelines recommend a high dose course (prednisone 1 mg/kg/day or up to 60-80 mg per day) for up to one month.

- A csDMARD is recommended if there is no response, or worsening, after two to four weeks of steroids. American Academy of Ophthalmology (AAO) guidelines recommend mycophenolate mofetil, azathioprine, methotrexate, cyclosporine, or tacrolimus. There is insufficient comparative evidence to conclude superiority of one csDMARD over another.
- Targeted DMARDs are recommended in patients who have had an inadequate response to corticosteroids and csDMARDs.
    * Adalimumab is FDA approved for uveitis and recommended as a treatment option in AAO guidelines. Adalimumab has been shown to lower flare rates and loss of visual acuity in two phase 3 RCTs in patients with active uveitis despite high-dose corticosteroids.
    * Infliximab is also a recommended treatment option for uveitis based on evidence from several comparative, open-label trials.

Cryopyrin-Associated Periodic Syndromes (CAPS)/Neonatal-Onset Multisystem Inflammatory Disease (NOMID)

- CAPS are a group of rare genetic diseases affecting approximately 200 to 300 people in the United States and are attributed to a specific genetic mutation. [61]
- Three types of CAPS affect the majority of patients: [61]
    * Neonatal-Onset Multisystem Inflammatory Disease (NOMID) – Urticaria-like rash, CNS involvement [papilledema, cerebrospinal fluid (CSF) pleocytosis, or sensorineural hearing loss], elevated C-reactive protein (CRP), or epiphyseal and/or patellar overgrowth on radiographs.
    * Familial Cold Auto-Inflammatory Syndrome (FCAS) – Recurrent intermittent episodes of fever and rash that primarily followed natural, artificial (e.g., air conditioning), or both types of generalized cold exposure.
    * Muckle-Wells Syndrome (MWS) – Syndrome of chronic fever and rash that may wax and wane in intensity and is sometimes exacerbated by generalized cold exposure. This syndrome may be associated with deafness or amyloidosis.
- Therapies that affect interleukin-1 (IL-1) may be helpful in controlling the symptoms of CAPS. [61]
    * Therapies that affect IL-1 include Kineret (anakinra), Arcalyst (rilonacept), and Ilaris (canakinumab), all of which have FDA marketing approval for one of more forms of CAPS. [62-64]
    * Due to the rarity of these conditions, it is difficult to conduct high-quality scientific studies.
- There have been no head-to-head trials comparing the efficacy of Kineret (anakinra), Arcalyst (rilonacept), or Ilaris (canakinumab) against each other or any other medication in the management of CAPS.
- The efficacy of Kineret (anakinra) was evaluated in a prospective, long-term, open-label and uncontrolled study in 43 patients with NOMID aged 0.7 to 46 years who were treated for up to 60 months. [62 65]

    * Treatment with Kineret (anakinra) resulted in improvements in all individual disease symptoms measured by a disease-specific Diary Symptom Sum Score (DSSS), as well as in the serum markers of inflammation.
    * For 11 patients who went through a withdrawal phase, disease symptoms and serum markers of inflammation worsened after withdrawal and promptly responded to reinstitution of Kineret (anakinra) therapy.

Cytokine Release Syndrome (CRS)

- Tocilizumab IV is FDA-approved for the treatment of cytokine release syndrome associated with the use of chimeric antigen receptor (CAR) T cell therapy, such as Kymriah (tisagenlecleucel) and Yescarta (axicabtagene ciloleucel). It is given as a one-time weight-based dose but up to three additional doses may be administered if there is no clinical improvement.
- Subcutaneous tocilizumab and sarilumab, another IL-6 inhibitor, have not been studied in cytokine release syndrome.

Safety Considerations

- In general, the overall safety profiles of targeted DMARDs for chronic inflammatory diseases is favorable. However, several have warnings related to infection risk and hypersensitivity reactions. [41 66-68] All are immunosuppressants and increase the risk of infection, though some drugs may increase the risk more than others.
- Certain products have unique safety concerns that should be factored into the overall risk-benefit profile.
- Oral JAK inhibitors (tofacitinib, upadacitinib, and baricitinib) contain a boxed warning for increased risk of serious infections, mortality, malignancies, major cardiovascular events, and thrombosis. In a post-marketing safety study, tofacitinib did not meet its primary endpoint of non-inferiority for risk of cardiovascular events and malignancy. Results showed that patients who received tofacitinib at either 5 mg or 10 mg twice daily had a higher rate of cardiovascular events and malignancy compared to patients who received a TNF inhibitor. Though the study only evaluated tofacitinib the warning has been extended to other JAK inhibitors used in the treatment of RA and other inflammatory diseases. [31 43 69-71]
    * The boxed warning is based on a safety study designed to evaluate the safety of tofacitinib relative to TNF inhibitors. The study included patients age 50 or older with at least one CV risk factor and all patients received background MTX. Patients were randomized to one of three groups: tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, or a TNF inhibitor.
    * The study failed to meet its pre-specified safety endpoint of non-inferiority to TNF inhibitors for risk of cardiovascular events and malignancy.
    * The prescribing information for each JAK inhibitors has been updated to clarify that each JAK inhibitor is only indicated for to certain patients who have not responded or cannot tolerate one or more TNF blockers. [43]
    * The FDA continues to investigate these safety concerns and will provide updates as additional information becomes is available.

    * The risks and benefits of JAK inhibitors in patients at risk for venous thromboembolism should be carefully considered when choosing treatment strategies.
- Olumiant (baricitinib) has a boxed warning describing an increased risk of venous thromboembolism. Due to this risk, the use of baricitinib is limited to patients who have failed prior treatment options. There are several alternative targeted agents for the treatment of RA that do not carry a risk for VTE and have longer records of safety experience with comparable or better efficacy than baricitinib.
- While newer agents such as IL-23 inhibitors and IL-17 inhibitors, have demonstrated favorable risk-benefit profiles in clinical studies there is limited long-term safety experience. Additionally, there is limited evidence directly comparing to existing standards of care. [41 66-68]
- New or worsening heart failure is listed as a warning and precaution for TNF inhibitors. A clinical trial evaluating etanercept for the treatment of heart failure was terminated early due to lack of efficacy and suggested higher morality in etanercept-treated patients compared to placebo. Post-market, new or worsening heart failure have been reported with TNF inhibitors.

Dose Escalation

- There are no randomized, controlled trials to support dose escalation of ustekinumab from every 8 to 12 weeks to every four-week dosing in any condition. It is uncertain if there is any additional benefit with increased dosing and there is limited long-term safety data.
    * The evidence supporting the use of every four weeks in CD is limited to retrospective, observational studies. [72 73] While some patients experienced disease remission, high-quality, prospective studies are needed to identify the ideal population and clarify the risk-benefit profile. Due to limited evidence supporting use, more frequent dosing of ustekinumab for CD is limited to patients who have had an inadequate response to every 8-week dosing.
    * There are no high-quality studies evaluating the use of every 4-week dosing of ustekinumab in PsO.
    * Additional studies are also needed to clarify the role of dose escalation versus standard dosing or other mechanisms of action.
- Guidelines do not currently support the use of therapeutic drug monitoring of ustekinumab to guide dose escalation.
    * There is very limited evidence on the efficacy of different maintenance troughs for ustekinumab. [74 75]
    * While therapeutic drug monitoring may play a role in the management of TNF inhibitors, the same concepts may not apply to ustekinumab due to its different mechanism of action and pharmacokinetic properties.
- Phase 3 clinical trials of Entyvio (vedolizumab) for UC and CD included maintenance dosing intervals of every 4 weeks and every 8 weeks (with a dose of 300 mg). The results demonstrated that the two maintenance doses produce in similar response rates. In

long-term extension studies some patients who had an inadequate response to every 8-week dosing were able to achieve a response or regain response after increasing to every four-week dosing. Therefore, the use of every four-week dosing is limited to patients who have lost response or have had an inadequate response to every 8-week dosing. [76 77]

- In PsO, there was no statistically significant difference in response for patients who were dose escalated to secukinumab 300 mg every 2 weeks vs every 4 weeks in patients who had suboptimal response to standard dosing at 16 weeks. After 16 weeks, most patients who continued with a 4-week dosing interval were able achieve response. [78]
- Pharmacokinetic and exposure-response modeling suggest shortening the dosing interval for golimumab IV to every 6 weeks may ameliorate waning efficacy toward the end of the standard 8-week dosing interval experienced by a small proportion of patients. [69 79]

Appendix 1: Absolute and Relative Contraindications for Phototherapy/Photochemotherapy

History of melanoma or squamous-cell carcinoma
History of photosensitivity
Increased risk of photosensitivity due to concomitant disease state (e.g., porphyria, systemic lupus erythematosus) or chronic medication use (e.g., tetracycline or sulfonamide antibiotics)
Physical inability to stand for the required exposure time
Presence of premalignant lesions (e.g., actinic keratosis)
Presence of psoriatic arthritis
Treatment of facial or scalp lesions
Treatment of lesions in the groin area
Treatment of lesions on the palms of the hands or soles of the feet, or on nail beds
Type 1 or type 2 skin

Appendix 2: Select List of Conventional Synthetic Disease Modifying Anti-Rheumatic Drugs (csDMARDs)

Conventional Synthetic DMARDS for Rheumatic and Skin Conditions and Uveitis	
Azathioprine (AZA; Imuran)	Methotrexate (oral, injectable)*
Cyclosporine (CSA; Gengraf, Neoral, Sandimmune)*	Mycophenolate (MMF; CellCept, Myfortic)
Hydroxychloroquine (HCQ; Plaquenil)	Sulfasalazine (SSZ; Azulfidine)
Arava (leflunomide)	Soriatane (acitretin)*
Conventional Synthetic DMARDs for Gastrointestinal conditions	
Azathioprine (AZA; Imuran)	Mercaptopurine (6-MP; Purinethol)
Balsalazide (Colazal, Giazo)	Mesalamine (Apriso, Asacol HD, Delzicol, Lialda, Pentasa)
Cyclosporine (CSA; Gengraf, Neoral, Sandimmune)	Sulfasalazine (SSZ; Azulfidine)

*: Therapies used in the treatment of dermatologic conditions

Appendix 3: American College of Rheumatology (ACR) Classification Criteria for Establishing the Diagnosis of Rheumatoid Arthritis (RA) [77 78]

Diagnosis of RA requires the presence of at least 4 of 7 criteria below:
1. Morning stiffness in and around joints lasting more than 1 hour. 2. Arthritis in at least 1 area in a wrist or proximal interphalangeal (PIP) joint (hands or fingers) for > 6 weeks. 3. Simultaneous swelling or fluid accumulation in 3 or more joints for > 6 weeks. 4. Symmetric (bilateral joint) involvement for > 6 weeks. 5. Presence of rheumatoid nodules. 6. Positive serum rheumatoid factor. 7. Radiographic changes typical of RA (erosion or unequivocal bony decalcification in or adjacent to the involved joint) on hand and wrist present.

Appendix 4: American College of Rheumatology (ACR) Assessment Components for Improvement in Rheumatoid Arthritis (RA) [79]

- Tender joint count. - Swollen joint count. - Patient's assessment of pain. - Patient's global assessment of disease activity. - Physician's global assessment of disease activity. - Patient's assessment of physical function. - Acute phase reactant measures (erythrocyte sedimentation rate or C-reactive protein levels).

Appendix 5: American College of Rheumatology (ACR) Classification Criteria for Establishing the Diagnosis of Giant Cell Arteritis (GCA)

Diagnosis of GCA requires the presence of at least 3 of 5 criteria below:
1. Patient age 50 years or older. 2. New onset of localized headache. 3. Temporal artery tenderness or decreased temporal artery pulse. 4. Erythrocyte sedimentation rate of 50 mm per hour or greater. 5. Abnormal temporal artery biopsy.

Appendix 6: Example Contraindications to Self-Administered Therapy

The member is 13 years of age or younger.
Inability to self-inject due to significant behavioral issues and/or cognitive impairment including, but not limited to, those associated with developmental delay, down syndrome, dementia, or excessive anxiety such as needle phobia.
Preferred self-administered therapy/therapies are relatively contraindicated.

Cross References
Products with Therapeutically Equivalent Biosimilars/Reference Products, Medication Policy Manual, Policy No. dru620
Immune Globulin Replacement Therapy (IVIG, SCIG), Medication Policy Manual. Policy No. dru020
Interleukin-1 Antagonists, Medication Policy Manual, Policy No. dru677
Site of Care Review, Medication Policy Manual, Policy No. dru408

Codes	Number	Description
HCPCS	J3262	Injection, tocilizumab (Actemra IV), 1 mg
HCPCS	J0717	Injection, certolizumab pegol (Cimzia lyophilized powder vials), 1 mg
HCPCS	J3380	Injection, vedolizumab (Entyvio), 1 mg
HCPCS	J1602	Injection, golimumab (Simponi Aria), 1 mg, for intravenous use
HCPCS	J3245	Injection, tildrakizumab (Ilumya), 1 mg
HCPCS	J2327	Injection, risankizumab-rzaa (Skyrizi), intravenous, 1 mg
HCPCS	J3358	Ustekinumab (Stelara), for intravenous injection, 1 mg
HCPCS	J3357	Ustekinumab (Stelara), for subcutaneous injection, 1 mg
HCPCS	J0129	Injection, abatacept (Orencia), 10 mg
HCPCS	Q5133	Injection, tocilizumab-bavi (tofidence), 1 mg
HCPCS	Q5135	Injection, tocilizumab-aazg (tyenne), biosimilar, 1 mg
HCPCS	Q5137	Injection, ustekinumab-auub (wezlana), biosimilar, subcutaneous, 1 mg
HCPCS	Q5138	Injection, ustekinumab-auub (wezlana), biosimilar, intravenous, 1 mg

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Revision History

Revision Date	Revision Summary
12/16/2024	Effective 1/1/2025 • Policy updated to reflect the name change of Washington State Rx Services to ArrayRx.
9/19/2024	Effective 01/01/2025 • Moved Actemra (tocilizumab) IV to non-preferred for all applicable indications. • Added new Stelara (ustekinumab) biosimilars Pyzchiva, Selarsdi, and Wezlana to policy as non-preferred options.
9/19/2024	Effective 12/1/2024 • Added Tremfya (guselkumab) IV induction as a preferred provider-administered option for ulcerative colitis ahead of anticipated FDA approval. • Added Skyrizi (risankizumab) IV induction as a preferred provider-administered option for ulcerative colitis.
6/20/2024	• Updated authorization limit wording for Simponi Aria in *Table 1* for clarity. No change to intent. • Added new Spevigo (spesolimab) SC formulation to policy criteria and quantity limit for a loading dose in GPP maintenance. • Added Tofidence IV (tocilizumab-bavi) to policy as non-preferred. • Added Tyenne IV (tocilizumab-aazg) to policy as preferred. • Added investigational dose escalation language for Cosentyx (secukinumab).
3/21/2024	Effective 4/1/2024 • Updated Avsola (infliximab) and Stelara (ustekinumab) as preferred products. • Added Omvoh (mirikizumab) as a non-preferred product for ulcerative colitis (UC). • Updated background to include pouchitis and collagenous colitis. • Updated reference to Washington State Rx Services. Product list available at: https://www.hca.wa.gov/assets/pebb/ump-preferred-drug-list-2024.pdf
12/7/2023	• Updated new Cosentyx (secukinumab) IV formulation to policy criteria and QL for AS, nrSpA, and PsA. • Removed discontinued Cosentyx (secukinumab) lyophilized powder vials for subcutaneous administration.
09/14/2023	Updated Actemra (tocilizumab) criteria for use in cytokine release syndrome (CRS). Requirement changed to diagnosis only. CRS no longer need be chimeric antigen receptor (CAR) T-cell induced for coverage approval.

Revision Date	Revision Summary
3/16/2023	Updated reference to Washington State Rx Services. Product list available at: https://www.hca.wa.gov/assets/pebb/ump-preferred-drug-list-2023.pdf
12/9/2022	Effective 1/19/2023: • Updated diagnostic requirements for systemic juvenile idiopathic arthritis (SJIA). Now requires disease activity for at least 6 weeks instead of 6 months. • Skyrizi (risankizumab) quantity limit updated to include new 180 mg maintenance dose for Crohn's Disease (CD). • Updated preferred self-administered products to include Rinvoq (upadacitinib), Xeljanz/Xeljanz XR (tofacitinib), Skyrizi (risankizumab) in their respective indications. • Added Spevigo (spesolimab) to the policy for generalized pustular psoriasis (GPP) as a provider-administered option.
8/29/2022	Effective 10/1/2022: • Added Skyrizi (risankizumab) to policy as a preferred provider administered option for Crohn's disease. • Updated references to Products with Therapeutically Equivalent Biosimilars/Reference Products dru620 (dru905 archived effective 7/15/2022). • Updated cross references and HCPCS codes.
5/23/2022	Effective 7/1/2022: • Updated policy to allow dosing escalation of Simponi Aria (golimumab) to every 6 weeks. • Added Actemra (tocilizumab) IV to policy for Giant Cell Arteritis (GCA). • Updated Entyvio (vedolizumab) for Crohn's Disease (CD) and Ulcerative Colitis (UC) as a preferred provider-administered option. • Added HCPCS codes for provider-administered products.

Revision Date	Revision Summary
2/22/2022	Effective 3/13/2022: • Added coverage criteria for intravenous Actemra (tocilizumab) for solid organ transplant, antibody mediated rejection (AMR). • Added criteria to allow coverage of intravenous Orencia (abatacept) for *prophylaxis* of graft versus host disease (GVHD). • Added coverage criteria for Cosentyx (secukinumab) for enthesitis-related arthritis (ERA). • Wording for intravenous Actemra (tocilizumab) criteria for cytokine release syndrome (CRS) was modified to allow for coverage as part of CAR-T treatment plan. • Updated position statement to clarify that non-TNFs may be an option for New York Heart Association (NYHA) class III/IV heart failure (HF) based on guidelines and post-market reports of new or worsening HF with TNF inhibitors.
10/15/2021	• Revised preferred infliximab products and clarified that they are reviewed under Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru905. • Added unbranded Janssen infliximab product to policy as non-preferred.
7/16/2021	Updated appendix numbers in criteria. No other changes.
4/21/2021	• Added coverage criteria for sarcoidosis and Takayasu Arteritis. • Updated investigational uses.
2/22/2021	Removed requirement for step therapy with two prior self-administered products prior to approval of infliximab products (Remicade and biosimilars).
10/28/2020	• Added Simponi Aria as a provider-administered option for polyarticular juvenile idiopathic arthritis (PJIA), a newly approved FDA indication. • Increased authorization limit for infliximab in immune-mediated colitis to two infusions. • Clarified that Cosentyx (secukinumab) vials are a provider-administered option for non-radiographic axial spondyloarthritis.

Revision Date	Revision Summary
8/25/2020	Effective 10/1/2020: • Revised clinical documentation requirements. • Updated quantity limits for Cimzia (certolizumab) based on newly FDA approved indication. • Removed references to appendix 2 in policy criteria and listed requirements for prior conventional therapies directly in criteria. • **Non-Radiographic Axial Spondyloarthritis:** New diagnosis category in policy. • **Chronic Plaque Psorasis:** - Non-biologic-step-therapy requirements changed from "BSA ≥ 10% AND phototherapy AND conventional DMARD" to "BSA ≥ 10% OR phototherapy OR conventional agent." - Conventional agent list expanded from just DMARDs to also include treatments such as topical corticosteroids. • **Hidradenitis Suppurativa:** - Removed requirement for disease severity. - Removed requirement for functional impairment. - Expanded list of acceptable step therapies from only antibiotics to also include corticosteroids, hormonal therapies, metformin, and retinoids. • **Systemic juvenile idiopathic arthritis:** Expanded list of acceptable step therapies from only conventional DMARDs to also include NSAIDs. • **Uveitits:** Expanded list of acceptable step therapies from only systemic corticosteroids to also include periocular intravitreal corticosteroids.
4/22/2020	• Updated quantity limits for Cosentyx (secukinumab) in axial Spondyloarthritis/ankylosing spondylitis. • Clarified that quantity limits for Cosentyx (secukinumab) in this policy apply to vials. Cosentyx (secukinumab) syringes are considered self-administered. • Updated biosimilar list to include Abrilada (adalimumab-afzb) and Avsola (infliximab-axxq). • Updated dosing for Stelara (ustekinumab) in ulcerative colitis. • Added COT language.
10/23/2019	New UMP-specific policy replacing dru444 for those members. Effective 1/1/2020.

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UMP Medication Policy Manual

Policy No: dru901

Topic: Tysabri, natalizumab (UMP plans)

Date of Origin: January 1, 2020

Committee Approval Date: March 16, 2023

Next Review Date: 2023

Effective Date: April 15, 2023

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Tysabri (natalizumab) is a medication used to treat multiple sclerosis or Crohn's disease. It is administered intravenously and works on the immune system to relieve symptoms of disease.

This policy applies to the Washington State Health Care Authority (HCA) Uniform Medical Plan (UMP) only. The UMP is a self-funded health plan offered through the Washington State HCA's Public Employees Benefits Board (PEBB) Program and School Employees Benefits Board (SEBB) Program and administered by Regence BlueShield.

Policy/Criteria

I. Continuation of therapy (COT): Tysabri (natalizumab) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, full policy criteria must be met for coverage.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Tysabri (natalizumab) may be considered medically necessary when criterion A below is met.

A. At least one of the following diagnostic criterion 1 or 2 below is met.

1. **Multiple sclerosis:** Initial authorization for Tysabri (natalizumab) may be considered medically necessary when criteria a and b below are met.

a. A definitive diagnosis of a **relapsing form of multiple sclerosis** [clinically isolated syndrome (CIS), relapsing-remitting MS (rrMS), or active secondary progressive MS (SPMS)] that has been established by or in consultation with a specialist in neurology or multiple sclerosis (see *Appendix A* for *American Academy of Neurology* multiple sclerosis definitions).

AND

b. Criteria i or ii below is met.

i. At least two self-administered disease modifying therapies for multiple sclerosis have been documented in clinical notes to be ineffective, not tolerated, or contraindicated (including, but not limited to, those situations in *Appendix C*):

Preferred Self-Administered Therapies (for UMP Members): (Please refer to coverage policies administered by Washington State Rx Services)
Aubagio (teriflunomide)
Avonex (interferon beta-1a)
dimethyl fumarate
fingolimod
glatiramer acetate
Vumerity (diroximel fumarate)

See Appendix B for other MS disease modifying therapies (DMTs)

Ineffectiveness is defined as meeting at least one of the following three criterion (1, 2, or 3) during treatment with one of these medications:

1. The patient continues to have clinical relapses (at least one relapse within the past 12 months).

OR

2. The patient continues to have CNS lesion progression as measured by MRI.

OR

3. The patient continues to have worsening disability. Examples of worsening disability include, but are not limited to, decreased mobility, decreased ability to perform activities of daily living due to disease progression, or an increase in EDSS score.

OR

ii. The patient has had a particularly aggressive initial disease course, as defined by meeting at least one of the following:

1. An EDSS score of ≥ 4 within 5 years of onset.

OR

2. Multiple (two or more) relapses with incomplete resolution in the past year.

OR

3. At least two MRI studies showing new or enlarging T2 lesions or gadolinium-enhancing lesions despite treatment over 6 months.

OR

4. The presence of spinal or brainstem lesions on MRI.

OR

2. Crohn's disease: Initial authorization for Tysabri (natalizumab) may be considered medically necessary for patients meeting all of the following criteria a, b, and c below.

a. Tysabri (natalizumab) is prescribed by, or in consultation with, a specialist in gastroenterology for the indication of Crohn's disease.

AND

b. Humira (adalimumab) is not effective after at least an initial 3-dose induction period, except if not tolerated due to documented clinical side effects.

AND

c. Infliximab is not effective after at least an initial induction period (5 mg/kg on weeks 0, 2 and 6), except if not tolerated due to documented clinical side effects.

III. Administration, Quantity Limitations, and Authorization Period

A. Pharmacy Services considers Tysabri (natalizumab) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Tysabri (natalizumab) may be authorized in quantities up to one 300-mg infusion every 4 weeks.

C. Authorization period:

1. Multiple sclerosis: Authorization may be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

2. Crohn's disease: Initial authorization shall be reviewed at 12 weeks. Subsequent authorization shall be reviewed at least every six months. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

IV. Tysabri (natalizumab) is considered not medically necessary when used in the following settings:

A. For the treatment of multiple sclerosis when used concomitantly with other disease-modifying multiple sclerosis therapies (MS DMTs) (see *Appendix B*).

B. For the treatment of Crohn's disease when used concomitantly with any of the following:

1. Adalimumab (Humira or biosimilars).

OR

2. Infliximab.

OR

3. Cimzia (certolizumab pegol).

C. For the treatment of ulcerative colitis.

V. Tysabri (natalizumab) is considered investigational when used for all other conditions, including, but not limited to:

A. Primary progressive multiple sclerosis (PPMS).

B. Rheumatoid arthritis.

Position Statement

Summary

- Tysabri (natalizumab) is a monoclonal antibody used: [1]
  - As monotherapy for the treatment of patients with relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations and delay the accumulation of physical disability.
  - For inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease (CD) with evidence of inflammation when there has been inadequate response to, or intolerance of, conventional CD therapies and TNF-α inhibitors.
- The intent of the policy is to allow coverage of Tysabri (natalizumab) in patients who failed two preferred disease modifying therapies for MS or as a first-line option in situations where the benefits outweigh the risks. Tysabri (natalizumab) may also be covered in patients with CD who have previously tried adalimumab or infliximab.
- Tysabri (natalizumab) may be used in patients who failed prior disease modifying therapy or as a first-line option in situations where the benefits outweigh the risks. [1,2]
  - Tysabri (natalizumab) contains a Boxed Warning describing an increased risk of progressive multifocal leukoencephalopathy (PML) with its use.
  - Because of these safety concerns, distribution of Tysabri (natalizumab) is restricted. Only prescribers registered in the CD TOUCH or MS TOUCH programs may prescribe Tysabri (natalizumab) for CD or MS, respectively.

- Tysabri (natalizumab) is considered a disease modifying therapy (DMT) for multiple sclerosis. Other disease modifying multiple sclerosis treatments include interferon beta products (Avonex, Rebif, Betaseron, Extavia, or Plegridy), fingolimod (generic, Gilenya, and Tascenso ODT), glatiramer acetate (Copaxone, Glatopa), Aubagio (teriflunomide), dimethyl fumarate, Ocrevus (ocrelizumab), Briumvi (ublituximab-xiiy), and Lemtrada (alemtuzumab). [2] Rituximab may also be used off label for the treatment of relapsing forms of MS. [1]
- Tysabri (natalizumab) may be used as initial disease modifying therapy in patients with "aggressive" or highly active disease." Definitions for highly active disease are not well established however measures often include relapsing activity, MRI markers, or the location of gadolinium-enhancing lesions. The goal of treatment in patients with aggressive disease is initiate treatment with a highly effective therapy before the patient suffers permanent disability. [2]
- Monitoring for disease activity on MRI is recommended every 6 months.
- Tysabri (natalizumab) is considered a disease modifying Crohn's disease treatment. Other disease modifying Crohn's disease treatments include Humira (adalimumab), infliximab, Cimzia (certolizumab pegol), Entyvio (vedolizumab), and Stelara (ustekinumab).
- No studies have shown that the efficacy of Tysabri (natalizumab) is superior to other disease modifying therapies in the treatment of either multiple sclerosis or Crohn's disease.
- It is not recommended that Tysabri (natalizumab) be administered concomitantly with other disease-modifying MS medications due to the potential for increased risk of serious adverse events.
- Tysabri (natalizumab) is approved at the dose of 300 mg infused intravenously over approximately one hour, every 28 days in the treatment of multiple sclerosis or Crohn's disease. The safety and efficacy of Tysabri (natalizumab) at doses higher than 300 mg every 28 days have not been adequately evaluated.

Clinical Efficacy

MULTIPLE SCLEROSIS

- A 2015 Cochrane network meta-analysis concluded that Lemtrada (alemtuzumab), Tysabri (natalizumab), fingolimod (generic, Gilenya, and Tascenso ODT), and mitoxantrone are more effective than other drugs at preventing relapse than other agents based on moderate to high quality evidence. The authors also concluded that only Tysabri (natalizumab) shows a beneficial effect on disability progression based on moderate quality data. Lemtrada (alemtuzumab) and mitoxantrone were also found to be more effective than other treatments at slowing disability progression but the quality of evidence was lower. [3] Tysabri (natalizumab) has only been shown to be safe and effective in the treatment of relapsing forms of multiple sclerosis. [1] There are no data to support the use of Tysabri (natalizumab) in non-relapsing forms of multiple sclerosis.
- American Academy of Neurology guidelines state disease modifying therapies should be offered to patients with relapsing forms of MS. The choice of initial agent should be individualized to incorporate of safety, route of administration, lifestyle, cost, efficacy,

common adverse effects (AEs), and tolerability. Disease activity, adherence, AE profiles, and mechanism of action should be considered when switching disease modifying therapies. [2]

- AAN guidelines state that Tysabri (natalizumab), fingolimod (generic, Gilenya, Tascenso ODT), or Lemtrada (alemtuzumab) should be used in patients with highly active disease. [2]
- Although no specific guidelines exist, proposed definitions of aggressive or highly active have been developed. It may be defined as at least one of the following: an EDSS score of 4 within 5 years of onset, multiple (two or more) relapses with incomplete resolution over a one-year period, more than two MRI studies showing new or enlarging T2 lesions or gadolinium-enhancing lesions despite treatment, no response to therapy with one or more disease modifying therapies for up to 1 year, or the presence of spinal lesions. Monitoring for treatment efficacy via MRI is recommended every 6 months. [4]
- Tysabri (natalizumab) in combination with any other disease modifying multiple sclerosis treatment medication has not been shown to be more effective than Tysabri (natalizumab) alone in the treatment of multiple sclerosis and may be contraindicated due to safety concerns.

CROHN'S DISEASE

- FDA-approval of Tysabri (natalizumab) in Crohn's Disease (CD) was based on three trials; two in induction of clinical response/remission and one in the maintenance of remission. [1]
    * Patients in the induction trials had moderately to severely active CD (Crohn's Disease Activity Index [CDAI] $\geq$ 220 and $\leq$ 450).
    * In one of the two induction studies, significant differences in response to Tysabri (natalizumab) were only observed in the subgroup of patients with elevated C-reactive protein (CRP) levels. The second induction study used elevated CRP as an entry criterion. However, other medications (e.g., prednisone) may lower CRP levels, making this an insensitive predictor of efficacy.
    * The treatment effect in the induction studies ranged from approximately 13 to 15%.
    * In the trial that looked at maintenance of response of CD over 9 to 15 months, the treatment effect was approximately 33%.
- Concomitant use Tysabri (natalizumab) with immunosuppressives (6-mercaptopurine, azathioprine, cyclosporine, and methotrexate) or inhibitors of TNF-α (e.g., infliximab and adalimumab) is not recommended due to potential safety concerns . [1]
- Tysabri (natalizumab) is generally considered a last-line agent for Crohn's disease due to lack of comparative efficacy with other therapies and its potential for serious safety risks.
    * Steroids, immunosuppressives, and inhibitors of TNF-alpha are recommended prior to prescribing Tysabri (natalizumab).

    * A study demonstrating the efficacy of Humira (adalimumab) in patients in whom infliximab was not effective is the basis for recommending both Humira (adalimumab) and infliximab prior to Tysabri (natalizumab).
        ▪ A randomized, placebo-controlled study comparing Humira (adalimumab) with placebo in 325 patients with Crohn's disease who had lost response to treatment with, or were intolerant to, previous infliximab therapy demonstrated induction of remission in 21% versus 7% of patients who had received adalimumab and placebo, respectively ($p<0.001$, ABI 14%, NNT=8). [5]
- One small trial (n = 79) studied the concomitant use of Tysabri (natalizumab) and infliximab in patients who did not achieve remission of their CD after 12 weeks of infliximab. [6]
    * The trial was not powered to detect differences in efficacy between treatment groups.
    * There were not enough patients in the study to determine whether there were differences in uncommon or rare adverse effects between treatment groups.
    * The Tysabri (natalizumab) prescribing information warns against use of this combination.
- Tysabri (natalizumab) should be discontinued in patients with CD who: [1]
    * Do not achieve therapeutic benefit after 12 weeks of induction therapy.
    * Cannot discontinue chronic concomitant steroids within six months of starting therapy.

Safety

- Several cases of progressive multifocal leukoencephalopathy (PML), a progressive demyelinating disease of the CNS, have been associated with Tysabri (natalizumab) use. PML is an opportunistic viral infection of the brain that usually leads to death or severe disability. [1]
- The Tysabri (natalizumab) prescribing information contains a Boxed Warning describing the increased risk of PML, which may lead to death or severe disability. [1]
- Because of the risk of PML, distribution of Tysabri (natalizumab) is restricted via the TOUCH Prescribing Program.
    * Providers must register to prescribe, distribute, or infuse natalizumab.
    * Only patients who are registered with and who meet all the conditions of either the MS or CD TOUCH programs are eligible to receive natalizumab.
- The most common side effects observed in patients receiving Tysabri (natalizumab) include: infections, acute hypersensitivity reactions, depression, and cholelithiasis (gall stones). [1]
- There are several case reports of patients who developed melanoma after starting treatment with Tysabri (natalizumab). [7] Although cause-effect has not been established, clinicians should be aware of this potential risk, especially when considering therapy for patients with a history of melanoma.

- The Tysabri (natalizumab) prescribing information contains a warning regarding the potential for liver injury. In some patients this occurred as early as six days after an initial dose. [1]

Dosing and administration

- Tysabri (natalizumab) is administered as an intravenous infusion (300 mg) once every 28 days in the treatment of multiple sclerosis and Crohn's disease. The safety and efficacy of Tysabri (natalizumab) at doses higher than 300 mg every 28 days have not been adequately evaluated. [1]

Natalizumab – Use in Other Conditions

- The TOUCH Prescribing Program currently prevents off-label use of Tysabri (natalizumab).
- Authors of a small, open-label study in 10 patients with active ulcerative colitis reported clinical benefit at 4 weeks with administration of Tysabri (natalizumab). Larger, well-designed trials are needed before safety and efficacy are established for this indication.[8]
- There are no data available to support the safety and efficacy of Tysabri (natalizumab) in the treatment of rheumatoid arthritis.

Appendix A: Multiple Sclerosis Forms/Clinical Course Definitions [1,9]	
Clinically Isolated Syndrome (CIS)	The first clinical presentation that shows characteristics of inflammatory demyelination that could be MS.
Relapsing-remitting (RRMS)	Characterized by acute relapses that are followed by some degree of recovery. These attacks develop acutely, evolving over days to weeks. Over the next several weeks to months, most patients experience a recovery of function that is often (but not always) complete. Between attacks the patient is neurologically and symptomatically stable.
Secondary progressive (SPMS)	Defined as sustained progression of physical disability occurring separately from relapses, in patients who previously had RRMS. SPMS may be active or not active. Activity is determined by the presence of ongoing relapses or MRI activity. There are no clinical, imaging, immunologic, or pathologic criteria to determine when a patient transition from RRMS to SPMS, it is usually diagnosed retrospectively.
Primary progressive (PPMS)	Defined as progression of disability from onset without superimposed relapses. The AAN defines PPMS as the third clinical type characterized by a steady decline in function from the beginning without acute attacks.

Appendix B: Disease-Modifying Agents Used in the Treatment of Multiple Sclerosis (MS DMTs)
Aubagio (teriflunomide)
Briumvi (ublituximab-xiiy)
Dimethyl fumarate
Fingolimod (generic, Gilenya, Tascenso ODT)
Glatiramer acetate (Copaxone, Glatopa)
Interferon beta-1a* (Avonex, Rebif)
Interferon beta-1b* (Betaseron, Extavia)
Lemtrada (alemtuzumab)
Mavenclad (cladribine)
Mayzent (siponimod)
Mitoxantrone
Ocrevus (ocrelizumab)
Plegridy (peginterferon beta-1a)
Rituximab [1]
Tysabri (natalizumab)
Vumerity (diroximel fumarate)

[1] Rituximab is not FDA-approved for use in MS, but has evidence for efficacy.

Appendix C: Example Contraindications to Self-Administered Therapy
The member is 13 years of age or younger.
Inability to self-inject due to significant behavioral issues and/or cognitive impairment including, but not limited to, those associated with developmental delay, down syndrome, dementia, or excessive anxiety such as needle phobia.
Preferred self-administered therapy/ therapies are relatively contraindicated.

Cross References
Products with Therapeutically Equivalent Biosimilars/Reference Products, Medication Policy Manual, Policy No. dru620
Provider-administered drugs for chronic inflammatory diseases (UMP Plans), Medication Policy Manual, Policy No. dru900
Ocrevus, ocrelizumab (UMP Plans), Medication Policy Manual, Policy No. dru902
Briumvi, ublituximab-xiiy (UMP plans), Medication Policy Manual, Policy No. dru907
Lemtrada, alemtuzumab (UMP plans), Medication Policy Manual, Policy No. dru903

Codes	Number	Description
HCPCS	J2323	Injection, natalizumab (Tysabri), 1 mg
ICD-10	G35	Multiple Sclerosis

References

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2. Rae-Grant, A, Day, GS, Marrie, RA, et al. Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. 2018;90:777-88. PMID: 29686116
3. Tramacere, I, Del Giovane, C, Salanti, G, D'Amico, R, Filippini, G. Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: a network meta-analysis. *The Cochrane database of systematic reviews*. 2015 Sep 18;9:CD011381. PMID: 26384035
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7. Mullen, JT, Vartanian, TK, Atkins, MB. Melanoma complicating treatment with natalizumab for multiple sclerosis. *The New England journal of medicine*. 2008;358:647-8. PMID: 18256405
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9. Goodin, DS, Frohman, EM, Garmany, GP, Jr., et al. Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. *Neurology*. 2002 Jan 22;58(2):169-78. PMID: 11805241

Revision History

Revision Date	Revision Summary
3/16/2023	Updated Appendix B and Cross References.
12/9/2022	• Updated Preferred Self-Administered Therapies (for UMP Members). • Updated Appendix B.
12/28/2021	Updated Preferred Self-Administered Therapies (for UMP Members).
10/15/2021	Removed Site of Care requirements. Updated document to only reference "infliximab" and not any brand product in particular.
1/20/2021	Updated Preferred Self-Administered Therapies (for UMP Members).
1/22/2020	Added continuation of therapy (COT) criteria (no change to intent of coverage criteria).
10/23/2019	New UMP-specific policy replacing dru111 for those members. Effective 1/1/2020.

Drug names identified in this policy are the trademarks of their respective owners.

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UMP Medication Policy Manual

Policy No: dru902

Topic: Ocrevus, ocrelizumab (UMP plans)

Date of Origin: January 1, 2020

Committee Approval Date: March 16, 2023

Next Review Date: 2023

Effective Date: April 15, 2023

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Ocrevus (ocrelizumab) is an intravenously administered medication indicated for the treatment of relapsing or primary progressive forms of multiple sclerosis. It works by destroying certain immune cells that are involved in the multiple sclerosis immune response.

This policy applies to the Washington State Health Care Authority (HCA) Uniform Medical Plan (UMP) only. The UMP is a self-funded health plan offered through the Washington State HCA's Public Employees Benefits Board (PEBB) Program and School Employees Benefits Board (SEBB) Program and administered by Regence BlueShield.

Policy/Criteria

I. Continuation of therapy (COT): Ocrevus (ocrelizumab) may be considered medically necessary for COT when criterion A, B, or C **AND** D below is met.

A. For diagnoses NOT listed in the coverage criteria below, full policy criteria must be met for coverage.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

AND

D. Site of care administration requirements are met [refer to Medication Policy Manual, *Site of Care Review*, dru408].

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Ocrevus (ocrelizumab) may be considered medically necessary when criteria A and B below are met:

A. Site of care administration requirements are met [refer to Medication Policy Manual, *Site of Care Review*, dru408].

AND

B. Criterion 1 or 2 below are met.

1. A definitive diagnosis of **primary progressive multiple sclerosis** (PPMS) has been established by a specialist in neurology or multiple sclerosis.

OR

2. Criteria a and b below are met.

a. A definitive diagnosis of a relapsing form of multiple sclerosis [clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), or active secondary progressive MS (SPMS)] has been established by a specialist in neurology or multiple sclerosis.

AND

b. Criteria i or ii below are met.

i. At **least two** self-administered disease modifying therapies for multiple sclerosis have been documented in clinical notes to be ineffective, not tolerated, or contraindicated (including, but not limited to, those situations in *Appendix B*):

Preferred Self-Administered Therapies (for UMP Members): (Please refer to coverage policies administered by Washington State Rx Services)
Aubagio (teriflunomide)
Avonex (interferon beta-1a)
dimethyl fumarate
fingolimod
glatiramer acetate
Vumerity (diroximel fumarate)

See Appendix A for other MS disease modifying therapies (DMTs)

Ineffectiveness is defined as meeting at least **one** of the following three criterion (1, 2, or 3) during treatment with one of these medications:

1. The patient continues to have clinical relapses (at least one relapse within the past 12 months).

OR

2. The patient continues to have CNS lesion progression as measured by MRI.

OR

3. The patient continues to have worsening disability. Examples of worsening disability include, but are not limited to, decreased mobility, decreased ability to perform activities of daily living due to disease progression, or an increase in EDSS score.

OR

ii. The patient has had a particularly aggressive initial disease course, as defined by meeting at least one of the following:

1. An EDSS score of ≥ 4 within 5 years of onset.

OR

2. Multiple (two or more) relapses with incomplete resolution in the past year.

OR

3. At least two MRI studies showing new or enlarging T2 lesions or gadolinium-enhancing lesions despite treatment over 6 months.

OR

4. The presence of spinal or brainstem lesions on MRI.

III. Administration, Quantity Limitations, and Authorization Period

A. Pharmacy Services considers Ocrevus (ocrelizumab) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Ocrevus (ocrelizumab) shall be authorized in quantities up to 1200 mg every 12 months (one infusion of 300 mg on day 1 followed by a second infusion on day 15 with subsequent doses of 600 mg infusions every 6 months thereafter).

C. Authorization may be reviewed at least annually to confirm that current medical necessity criteria are met and that the medication is effective. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

IV. Ocrevus (ocrelizumab) is considered investigational when used for all other conditions, including but not limited to:

A. Use in combination with other disease-modifying multiple sclerosis therapies (see *Appendix A*).

B. Any cancer indication, including, but not limited to B-cell chronic lymphocytic leukemia.

C. Maintenance dosing more frequent than every 24 weeks.

D. Neuromyelitis optica spectrum disorders (NMOSD).

E. Rheumatoid arthritis.

Position Statement

Summary

- Ocrevus (ocrelizumab) is a monoclonal antibody used as monotherapy for the treatment of patients with primary progressive multiple sclerosis (PPMS) and relapsing forms of multiple sclerosis (MS).
- Ocrevus (ocrelizumab) is considered a disease modifying multiple sclerosis treatment. Other disease modifying multiple sclerosis treatments for relapsing forms of MS include Lemtrada (alemtuzumab), Briumvi (ublituximab-xiiy), interferon beta products (Avonex, Rebif, Betaseron, Extavia, or Plegridy), fingolimod, glatiramer acetate, Aubagio

(teriflunomide), and dimethyl fumarate. Rituximab may also be used off label for the treatment of relapsing forms of MS.[1]

- The intent of this policy is to allow coverage of Ocrevus (ocrelizumab) in patients with primary progressive MS or in patients with a relapsing form of MS who have tried two preferred disease modifying therapies for MS or who have a particularly aggressive disease course.
- Ocrevus (ocrelizumab) has not been studied in combination with other disease-modifying MS medications and it is therefore not recommended that Ocrevus (ocrelizumab) be administered concomitantly with other disease-modifying MS medications as efficacy and safety have not been established. Concomitant use of Ocrevus (ocrelizumab) with any other disease-modifying therapy for MS is considered investigational.
- Ocrevus (ocrelizumab) is an intravenously infused medication. The starting dose is 300 mg given on day one followed by 300 mg two weeks later. Thereafter, Ocrevus (ocrelizumab) is given every 6 months at a dose of 600 mg.
- The safety and effectiveness of Ocrevus (ocrelizumab) in conditions other than PPMS or relapsing forms of MS have not been established.

Clinical Efficacy in Multiple Sclerosis

- Ocrevus (ocrelizumab) has been shown to reduce elapse rate, slows disability progression, and slows worsening of disease based on MRI outcomes in patients with relapsing forms of MS. [2]
    * Two identical, 96-week studies (OPERA I and OPERA II), evaluated the effects of Ocrevus (ocrelizumab) compared to Rebif (interferon beta-1a) in patients with relapsing forms of MS. Ocrevus (ocrelizumab) was superior to interferon beta-1a in reducing annualized relapse and in slowing confirmed disability progression. On MRI, the patients in the Ocrevus (ocrelizumab) group had fewer new and/or enlarging T2 lesions, less T1 lesions, and a reduced rate of total brain volume loss relative to the Rebif (interferon beta-1a) group.
- Ocrevus (ocrelizumab) has been shown to slow disability progression, and slow the worsening of MRI outcomes in patients with PPMS. [3]
    * One 120-week study (ORATORIO), evaluated the effects of Ocrevus (ocrelizumab) relative to placebo in patients with PPMS. Ocrevus (ocrelizumab) was superior to placebo reducing the proportion of patients who had sustained 12-week confirmed disability progression. The treatment group also showed a significant decrease in T2 volume and showed significantly less brain volume loss on MRI.

Safety [4]

- Ocrevus (ocrelizumab) contains warnings for infusion reactions, infections, and risk of malignancy.
- Common adverse events include upper respiratory tract infections, infusion reactions, skin infections, and lower respiratory tract infections.

Dosing and Administration [4]

- Ocrevus (ocrelizumab) is administered as an intravenous (IV) infusion.
- The starting dose is 300 mg IV followed by 300 mg IV two weeks later. Subsequent doses of Ocrevus (ocrelizumab) are then given every 6 months at a dose of 600 mg IV as a single infusion.

Ocrevus (ocrelizumab) – Use in Other Conditions

- Due to a lack of published data, the use of Ocrevus (ocrelizumab) in conditions other than relapsing forms of MS and PPMS is considered investigational.
- While Ocrevus (ocrelizumab) has a similar mechanism of action to rituximab it has not been studied for the same indications. Thus, due to a lack of data, these conditions are considered investigational.

Neuromyelitis Optica Spectrum Disorders (NMOSD)

- Neuromyelitis optica spectrum disorders (NMOSD; previously known as Devic disease) are characterized by a combination of bilateral optic neuropathy and cervical myelopathy. While both NMOSD and MS are demyelinating diseases they are considered different diseases based on unique immunologic features and differences in imaging features, biomarkers, and neuropathology. [5]
- For acute attacks and relapses of NMOSD, treatment usually consists of intravenous glucocorticoids followed soon by plasmapheresis for refractory or progressive symptoms. For prevention of attacks, systemic immunosuppression with agents including azathioprine, mycophenolate mofetil, rituximab, and mitoxantrone has been used, given the evidence that humoral autoimmunity plays a role in the pathogenesis of NMO. [6,7]
- Rituximab has been shown to the frequency of NMOSD relapses and neurologic disability based on results from one systematic review. However, the optimal treatment regimen and duration have not been determined and additional long-term safety experience is needed to clarify the role of rituximab as a first-line option. [8]
- There is no published evidence to support the use of Ocrevus (ocrelizumab) for NMOSD.

Appendix A: Disease-Modifying Agents Used in the Treatment of Multiple Sclerosis (MS DMTs)
Aubagio (teriflunomide)
Briumvi (ublituximab-xiiy)
Dimethyl fumarate
Fingolimod (generic, Gilenya, Tascenso ODT)
Glatiramer acetate (Copaxone, Glatopa)
Interferon beta-1a* (Avonex, Rebif)
Interferon beta-1b* (Betaseron, Extavia)
Lemtrada (alemtuzumab)
Mavenclad (cladribine)
Mayzent (siponimod)
Mitoxantrone
Ocrevus (ocrelizumab)
Plegridy (peginterferon beta-1a)
Rituximab [1]
Tysabri (natalizumab)
Vumerity (diroximel fumarate)

[1] Rituximab is not FDA-approved for use in MS, but has evidence for efficacy.

Appendix B: Example Contraindications to Self-Administered Therapy
The member is 13 years of age or younger.
Inability to self-inject due to significant behavioral issues and/or cognitive impairment including, but not limited to, those associated with developmental delay, down syndrome, dementia, or excessive anxiety such as needle phobia.
Preferred self-administered therapy/ therapies are relatively contraindicated.

Cross References
Briumvi, ublituximab-xiiy (UMP plans), Medication Policy Manual, Policy No. dru907
Lemtrada, alemtuzumab (UMP plans), Medication Manual, Policy No. dru903
Site of Care Review, Medication Policy Manual, Policy No. dru408
Tysabri, natalizumab (UMP Plans), Medication Policy Manual, Policy No. dru901

Codes	Number	Description
HCPCS	J2350	Injection, ocrelizumab (Ocrevus), 1 mg
ICD-10	G35	Multiple sclerosis

References

1. Rae-Grant, A, Day, GS, Marrie, RA, et al. Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. 2018;90:777-88. PMID: 29686116
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6. Kleiter, I, Gahlen, A, Borisow, N, et al. Neuromyelitis optica: Evaluation of 871 attacks and 1,153 treatment courses. *Annals of neurology*. 2016 Feb;79(2):206-16. PMID: 26537743
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8. Damato, V, Evoli, A, Iorio, R. Efficacy and Safety of Rituximab Therapy in Neuromyelitis Optica Spectrum Disorders: A Systematic Review and Meta-analysis. *JAMA Neurol*. 2016;73:1342-8. PMID: 27668357

Revision History

Revision Date	Revision Summary
3/16/2023	Updated Appendix A and Cross References.
12/9/2022	• Updated Preferred Self-Administered Therapies (for UMP Members). • Updated Appendix A.
12/28/2021	Updated Preferred Self-Administered Therapies (for UMP Members).
1/20/2021	• Clarified quantity limit. • Updated Preferred Self-Administered Therapies (for UMP Members).
1/22/2020	Added continuation of therapy (COT) criteria (no change to intent of coverage criteria).
10/23/2019	New UMP-specific policy replacing dru479 for those members. Effective 1/1/2020.

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Regence

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UMP Medication Policy Manual

Policy No: dru903

Topic: Lemtrada, alemtuzumab (UMP plans)

Date of Origin: January 1, 2020

Committee Approval Date: March 16, 2023

Next Review Date: 2023

Effective Date: April 15, 2023

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Lemtrada (alemtuzumab) is a medication used in the treatment of relapsing forms of multiple sclerosis (MS). It may help to slow the progression of disability and reduce the number of clinical relapses associated with this condition.

PLEASE NOTE: This policy does NOT apply to alemtuzumab (Campath), which is used primarily in the treatment of cancer (leukemia).

This policy applies to the Washington State Health Care Authority (HCA) Uniform Medical Plan (UMP) only. The UMP is a self-funded health plan offered through the Washington State HCA's Public Employees Benefits Board (PEBB) Program and School Employees Benefits Board (SEBB) Program and administered by Regence BlueShield.

Policy/Criteria

I. Continuation of therapy (COT): Lemtrada (alemtuzumab) may be considered medically necessary for COT when criterion A, B, or C below is met.

A. For diagnoses NOT listed in the coverage criteria below, full policy criteria must be met for coverage.

OR

B. For diagnoses listed in the coverage criteria below, criteria 1 and 2 must be met:

1. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

2. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

OR

C. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission.

Please note*: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Lemtrada (alemtuzumab) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criteria A and B below are met.

A. A definitive diagnosis of a **relapsing form of multiple sclerosis** [clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), or secondary progressive MS (SPMS)] has been established by a specialist in neurology or multiple sclerosis (see *Appendix A* for *American Academy of Neurology* multiple sclerosis definitions).

AND

B. At **least two** self-administered disease modifying therapies for MS have been documented in clinical notes to be ineffective, not tolerated, or contraindicated (including, but not limited to, those in *Appendix B*):

Preferred Self-Administered Therapies (for UMP Members): (Please refer to coverage policies administered by Washington State Rx Services.)
Aubagio (teriflunomide)
Avonex (interferon beta-1a)
dimethyl fumarate
fingolimod
glatiramer acetate
Vumerity (diroximel fumarate)

See Appendix B for other MS disease modifying therapies (DMTs)

Ineffectiveness is defined as meeting at least **one** of the following three criteria (1, 2, or 3) during treatment with one of these medications:

1. The patient continues to have clinical relapses (at least one relapse within the past 12 months).

OR

2. The patient continues to have CNS lesion progression as measured by MRI.

OR

3. The patient continues to have worsening disability. Examples of worsening disability include, but are not limited to, decreased mobility, decreased ability to perform activities of daily living due to disease progression, or an increase in EDSS score.

III. Administration, Quantity Limitations, and Authorization Period

A. Pharmacy Services considers Lemtrada (alemtuzumab) coverable only under the medical benefit (as a provider-administered medication).

B. When pre-authorization is approved, Lemtrada (alemtuzumab) may be covered in the following quantities and for the following authorization periods:

1. Initial authorization (first treatment course; 5 doses): Up to 12 mg/day on five consecutive days in a 12-month period.

2. Second authorization (second treatment course; 3 doses): Following the first treatment course (of five doses), a second treatment course of up to 12 mg/day on three consecutive days in a 12-month period.

3. Additional Authorizations [additional treatment course(s); 3 doses]: Following the second treatment course (of three doses), subsequent treatment courses of 12 mg/day on three consecutive days may be administered in a 12-month period.

4. All subsequent courses must be administered at least 12 months after the last dose of the prior treatment course.

C. Authorization shall be reviewed every 12 months. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

IV. Lemtrada (alemtuzumab) is considered investigational when used:

A. Concomitantly with other DMTs for multiple sclerosis (see *Appendix B*).

B. For non-relapsing forms of MS, such as primary progressive MS (PPMS) or SPMS without active relapses.

V. Lemtrada (alemtuzumab) is considered investigational when used for all other conditions, including but not limited to:

A. Any cancer indication, including, but not limited to B-cell chronic lymphocytic leukemia (CLL).

B. Post-transplant antibody induction therapy.

C. For the treatment of clinically isolated syndrome (CIS).

Position Statement

- Several disease-modifying therapies are used in the treatment of relapsing forms of multiple sclerosis (MS). They help to decrease the number of clinical exacerbations associated with this condition and slow the progression of disability. Relapsing forms of MS include: clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), and active secondary progressive MS (SPMS).
- The intent of the policy is to allow coverage of Lemtrada (alemtuzumab) in patients who failed two prior preferred disease modifying therapies for MS.
- There are many disease-modifying therapies (DMTs) for the treatment of MS, as listed in Appendix A. Rituximab may also be used off label for the treatment of relapsing forms of MS. [1]
- American Academy of Neurology (AAN) guidelines state:
  * DMTs should be offered to patients with relapsing forms of MS.
  * The choice of initial DMT should be individualized to consider of safety, route of administration, lifestyle, cost, efficacy, adverse effects (AEs), and tolerability.
  * Disease activity, adherence, AE profiles, and mechanism of action should be considered when switching DMTs. [1]
  * Tysabri (natalizumab), fingolimod (generic, Gilenya, and Tascenso ODT), or Lemtrada (alemtuzumab) should be used in patients with highly active disease. [1]
- Individual responses and tolerability of DMTs are unpredictable and may vary between patients. If one DMT provides an inadequate response, another DMT may be effective.

- There is no reliable evidence of increased efficacy or safety of one interferon beta product over another in reducing the signs and symptoms of MS or slowing the progression of disease.
- The safety and effectiveness of combination use of disease modifying therapies for MS medications has not been established.
- Lemtrada (alemtuzumab) is not recommended as a first or second-line option due to serious safety concerns.
    * Lemtrada (alemtuzumab) has boxed warnings describing an increased risk of autoimmunity, infusion reactions, and malignancies with its use. The FDA labeling states that it should generally be reserved for patients who have had an inadequate response to two or more DMTs for MS.
    * Because of these safety concerns, distribution of Lemtrada (alemtuzumab) is restricted with a REMS program for prescribers, health care facilities, and pharmacies.
- Mavenclad (cladribine) is not recommend as a first-line option or for the treatment of CIS due to serious safety concerns of malignancy and teratogenicity. [2]

Clinical Efficacy: Lemtrada (alemtuzumab)

- Two, randomized, open-label, rater-blinded, 2-year, studies compared Lemtrada (alemtuzumab) with interferon beta-1a in patients with relapsing-remitting multiple sclerosis (RRMS). [3,4]
    * The CARE-MS I trial included previously untreated patients while CARE-MS II trial included patients who had at least one relapse while on an interferon beta product or glatiramer acetate.
    * In each trial, there was a statistically significantly lower annualized relapse rate for patients treated with Lemtrada (alemtuzumab) (22%-35%) compared to interferon beta-1a (40%-51%).
    * Treatment-experienced patients treated with Lemtrada (alemtuzumab) experienced a statistically significant reduction in the rate of disease progression compared to those treated with interferon beta 1a (13% vs 20%, p=0.008). The difference in rates of disease progression was not statistically significant among treatment-naïve patients.
- Extension studies for Lemtrada (alemtuzumab) suggest that efficacy is maintained through at least year five but certain patients with disease activity may require additional courses. Among patients who completed CARE-MS II, 58.0% received just no additional courses of Lemtrada (alemtuzumab) while 30.1% received one additional course at some point in the five-year follow-up period. The most common reason for additional courses was relapse. [5]
- Lemtrada (alemtuzumab) has not been directly compared to MS DMTs other than interferon beta-1a, nor has it been studied concomitantly with other DMTs.

Safety

- Lemtrada (alemtuzumab) [10]
  * Lemtrada (alemtuzumab) has boxed warnings for the following:
    - Sometimes fatal autoimmune conditions, such as immune thrombocytopenia and anti-glomerular basement membrane diseases.
    - Serious and life-threatening infusion reactions.
    - An increased risk of malignancies including thyroid cancer, melanoma and lymphoproliferative disorders.
  * Due to its significant safety concerns an FDA Risk Evaluation and Mitigation Strategy (REMS) program limits the availability of Lemtrada (alemtuzumab) to certified prescribers, healthcare facilities, and specialty pharmacies.
  * Regular monitoring is required due to the potential for long-term adverse events. Complete blood count, serum creatinine levels, urinalysis should be collected prior to treatment and at monthly intervals. Thyroid function tests should be conducted prior to treatment and every three months thereafter. Baseline and annual skin exams should be conducted to monitor for melanoma.

Investigational Uses – Lemtrada (alemtuzumab)

The Lemtrada REMS program mitigates off-label use of Lemtrada (alemtuzumab); however, it has been studied in other conditions. Due to a lack of published data, lack of high-quality data, or lack of positive data, these conditions are considered investigational. Details of select investigational uses are reported below.

- B-cell chronic lymphocytic leukemia
  * A high dose formulation of Campath (alemtuzumab) was approved for the treatment of B-cell chronic lymphocytic leukemia (CLL) but was removed from the market in 2012 to prevent off-label use of Campath in MS. Since 2012, Campath has been available for very limited use in CLL through patient access programs. Lemtrada (alemtuzumab) is given at a lower dose when used for MS, lower doses are considered investigational for any other condition, including CLL and other cancers.
  * There have been no controlled clinical trials evaluating the use of low-dose (12 mg) Lemtrada (alemtuzumab) in B-cell chronic lymphocytic leukemia. [11-13]
  * High dose Campath (alemtuzumab) is available for patients with leukemia directly from the manufacturer, free of charge through patient access programs.
- Post-transplant antibody induction therapy
  * There are no controlled clinical trials evaluating the use of low-dose (12 mg) Lemtrada (alemtuzumab) in the post-transplant setting. [14,15]
- The safety and effectiveness of Lemtrada (alemtuzumab) in combination with other disease-modifying MS therapies have not been adequately studied.

Appendix A: Multiple Sclerosis Forms/Clinical Course Definitions [1,9]	
Clinically Isolated Syndrome (CIS)	The first clinical presentation that shows characteristics of inflammatory demyelination that could be MS.
Relapsing-remitting (RRMS)	Characterized by acute relapses that are followed by some degree of recovery. These attacks develop acutely, evolving over days to weeks. Over the next several weeks to months, most patients experience a recovery of function that is often (but not always) complete. Between attacks the patient is neurologically and symptomatically stable.
Secondary progressive (SPMS)	Defined as sustained progression of physical disability occurring separately from relapses, in patients who previously had RRMS. SPMS may be active or not active. Activity is determined by the presence of ongoing relapses or MRI activity. There are no clinical, imaging, immunologic, or pathologic criteria to determine when a patient transition from RRMS to SPMS, it is usually diagnosed retrospectively.
Primary progressive (PPMS)	Defined as progression of disability from onset without superimposed relapses. The AAN defines PPMS as the third clinical type characterized by a steady decline in function from the beginning without acute attacks.

Appendix B: Disease-Modifying Agents Used in the Treatment of Multiple Sclerosis (MS DMTs)
Aubagio (teriflunomide)
Briumvi (ublituximab-xiiy)
Dimethyl fumarate
Fingolimod (generic, Gilenya, and Tascenso ODT)
Glatiramer acetate (Copaxone, Glatopa)
Interferon beta-1a* (Avonex, Rebif)
Interferon beta-1b* (Betaseron, Extavia)
Lemtrada (alemtuzumab)
Mavenclad (cladribine)
Mayzent (siponimod)
Mitoxantrone
Ocrevus (Ocrelizumab)
Plegridy (peginterferon beta-1a)
Rituximab [1]
Tysabri (natalizumab)
Vumerity (diroximel fumarate)

[1] Rituximab is not FDA-approved for use in MS, but has evidence for efficacy

Appendix C: Example Contraindications to Self-Administered Therapy
The member is 13 years of age or younger.
Inability to self-inject due to significant behavioral issues and/or cognitive impairment including, but not limited to, those associated with developmental delay, down syndrome, dementia, or excessive anxiety such as needle phobia.
Preferred self-administered therapy/ therapies are relatively contraindicated.

Cross References
Tysabri, natalizumab (UMP Plans), Medication Policy Manual, Policy No. dru901
Ocrevus, ocrelizumab (UMP Plans), Medication Policy Manual, Policy No. dru902
Briumvi, ublituximab-xiiy (UMP plans), Medication Policy Manual, Policy No. dru907

Codes	Number	Description
HCPCS	J0202	Injection, alemtuzumab (Lemtrada), 1 mg
ICD-10	G35	Multiple sclerosis

References

1. Rae-Grant, A, Day, GS, Marrie, RA, et al. Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. 2018;90:777-88. PMID: 29686116
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14. Farney, AC, Doares, W, Rogers, J, et al. A randomized trial of alemtuzumab versus antithymocyte globulin induction in renal and pancreas transplantation. *Transplantation*. 2009 Sep 27;88(6):810-9. PMID: 19920781
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Revision History

Revision Date	Revision Summary
3/16/2023	Updated Appendix B and Cross References.
12/9/2022	• Updated Preferred Self-Administered Therapies (for UMP Members). • Updated Appendix B.
12/28/2021	Updated Preferred Self-Administered Therapies (for UMP Members)
1/20/2021	• Clarified reauthorization period • Updated Preferred Self-Administered Therapies (for UMP Members)
1/22/2020	Added continuation of therapy (COT) criteria (no change to intent of coverage criteria).
10/23/2019	New UMP-specific policy replacing dru511 for those members. Effective 1/1/2020.

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UMP Medication Policy Manual **Policy No:** dru904

Topic: Non-preferred filgrastim products (UMP plans) **Date of Origin:** January 1, 2020

- Neupogen, filgrastim
- Nivestym, filgrastim-aafi
- Nypozi, filgrastim txid
- Releuko, filgrastim-ayow

Committee Approval Date: September 19, 2024 **Next Review Date:** 2025

Effective Date: December 1, 2024

IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of Medication Policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Filgrastim is a granulocyte-colony stimulating factor (G-CSF) that helps reduce the risk of infections in patients undergoing strong chemotherapy. Filgrastim is available as several different products. This policy applies to the non-preferred products only.

This policy applies to the Washington State Health Care Authority (HCA) Uniform Medical Plan (UMP) only. The UMP is a self-funded health plan offered through the Washington State HCA's Public Employees Benefits Board (PEBB) Program and School Employees Benefits Board (SEBB) Program and administered by Regence BlueShield.

Policy/Criteria

Most contracts require pre-authorization approval of non-preferred filgrastim products (as listed in Table 1) prior to coverage.

I. Continuation of therapy (COT): Continuation of therapy (COT): Non-preferred filgrastim products (as listed in Table 1) may be considered medically necessary for COT when full policy criteria below are met, including quantity limit.

Please note: *Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Non-preferred filgrastim products (as listed in *Table 1*) may be considered medically necessary when there is clinical documentation (including, but not limited to chart notes) that criterion A or B below are met.

A. Treatment with **all** preferred products (as listed in *Table 1*) have been ineffective, not tolerated, or contraindicated.

OR

B. Documented emergent clinical indication for filgrastim (see *Appendix 1*) **AND** there is attestation by the providing clinic that **all** preferred products (as listed in *Table 1*), are not available for same-day administration.

Table 1: Reference and Biosimilar Pegfilgrastim Products

	Product name	Formulary status
Reference Product	Neupogen (filgrastim)	Non-preferred/PA required
Biosimilars	Granix (tbo-filgrastim)	Preferred/No PA required [a]
	Zarxio (filgrastim-sndz)	Preferred/No PA required [a]
	Nivestym (filgrastim-aafi)	Non-preferred/PA required
	Releuko (filgrastim-ayow)	Non-preferred/PA required
	Nypozi (filgrastim txid)	Non-preferred/PA required

[a] As a preferred biosimilar, available for coverage without pre-authorization ("no PA required")

III. Administration, Quantity Limitations, and Authorization Period

A. Pharmacy Services considers all non-preferred filgrastim products (as listed in *Table 1*) coverable under the pharmacy benefit (as self-administered medications) OR coverable under the medical benefit (as provider-administered medications).

B. **Non-preferred product approval for unavailability of a preferred product:** Initial authorization will be for three months only. Continued authorization will not be considered solely for unavailability of a preferred product (Zarxio or Granix, as listed in *Table 1*).

C. **All other non-preferred product approvals**: Authorization **may** be reviewed at least annually. Clinical documentation (including, but not limited to chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.

Position Statement

Summary[1-6]

- The intent of this policy is to promote the use of biosimilar products that are the lowest overall cost. All filgrastim products are considered safe and effective options.
- This policy allows for:
  * Coverage of non-preferred filgrastim products when all of the preferred filgrastim products are ineffective, not tolerated, or contraindicated.
  * Coverage of non-preferred filgrastim products during an emergent clinical situation in which filgrastim is indicated, and the providing clinic does not have any of the preferred filgrastim products available for administration.
- There is no evidence that any one filgrastim product is safer or more effective than another. Among these products, preferred filgrastim provide the best value for members.
- Hospitals and health-systems have medication formularies developed independent of the health plan. The health plan is unable to cover more expensive products for the convenience of the hospital, health-system, provider, or member. Preferred biosimilar products represent the lowest cost to members and the plan; the use of more expensive products without evidence of superior efficacy or safety is not medically necessary per the member's contract.

Appendix 1:

Emergent clinical indications for filgrastim (same-day administration) [a]
Acute radiation syndrome.
Aplastic anemia.
Harvesting of peripheral blood stem cells.
Neutropenia (documented; including but not limited to febrile, chronic, chemotherapy-induced when given outside normal dosing schedule, agranulocytosis).
Patient is being discharged from an inpatient hospital stay and has a documented ongoing indication for filgrastim (filgrastim doses given as part of the inpatient stay is not subject to pre-authorization).

[a] The need for filgrastim in the FUTURE is not considered an "Emergent clinical indication," such as filgrastim for use with scheduled chemotherapy (not yet started).

Codes	**Number**	**Description**
HCPCS	J1442	Injection, filgrastim (Neupogen), excludes biosimilars, 1 microgram
HCPCS	Q5110	Injection, filgrastim-aafi (Nivestym), biosimilar, 1 microgram
HCPCS	Q5125	Injection, filgrastim-ayow, biosimilar, (Releuko), 1 microgram

References

1. Granix [prescribing information]. North Wales, PA: Teva; March 2019.
2. Neupogen [prescribing information]. Thousand Oaks, CA: Amgen; February 2021.
3. Nivestym [prescribing information]. Lake Forest, IL: Hospira/Pfizer; May 2021.
4. Zarxio [prescribing information]. Princeton, NJ: Sandoz; July 2021.
5. Releuko [prescribing information]. Bridgewater, NJ: Amneal Biosciences, LLC; February 2022.
6. Nypozi [prescribing information]. San Diego, CA: Tanvex BioPharma USA, Inc.; June 2024.

Revision History

Revision Date	Revision Summary
9/19/2024	Added Nypozi, filgrastim-txid to policy, a new biosimilar.
6/20/2024	No criteria changes with this annual review.
6/15/2023	No criteria changes with this annual update.
6/17/2022	• Added Releuko, filgrastim-ayow to policy, a new biosimilar. • Modify criteria wording, for operational clarity (no change to intent of the criteria with this annual update). • Addition of a product table, to delineate the preferred/non-preferred and reference product/biosimilars.
7/16/2021	No criteria changes with this annual update.
7/22/2020	Added continuation of therapy criteria. No change to intent of policy.
10/23/2019	New UMP-specific policy. Effective 1/1/2020. The intent of the policy is to cover non-preferred filgrastim products when preferred products are not a treatment option (ineffective, not tolerated, or contraindicated) or unavailable for administration for an emergent clinical indication.

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