

Uniform Medical Plan (UMP) coverage limits for drugs covered under UMP's prescription drug benefit

Updates effective November 01, 2025

These coverage limits apply to all UMP Plans that the Public Employees Benefits Board (PEBB) and the School Employees Benefits Board (SEBB) offer.

As a state-sponsored health plan, UMP follows the Washington State Pharmacy and Therapeutics (P&T) Committee's coverage recommendations. The committee consists of Washington health care professionals, including physicians and pharmacists. The UMP Preferred Drug List (PDL) aligns with the committee's coverage recommendations and contains useful information such as a drug's coverage limits. The UMP PDL is the same for both Public Employees Benefits Board (PEBB) and School Employees Benefits Board (SEBB) members.

The Washington State P&T committee does not review all drug classes. For all other prescription drug classes, the ArrayRx P&T Committee makes coverage recommendations for UMP to consider. UMP then determines a drug's coverage, including any coverage limits. These drugs are also included on the UMP PDL.

Some prescription drugs require preauthorization to determine whether they are medically necessary and meet UMP coverage criteria. If you do not receive approval for your preauthorization, UMP will not cover these drugs. **To request a preauthorization, a member, pharmacy, or prescribing provider can call ArrayRx at 1-888-361-1611 (TRS: 711).**

Some drugs may only be covered under UMP medical benefits and have different rules for preauthorization. To request a preauthorization for a drug covered under UMP medical benefits, call UMP Customer Service at:

- PEBB Members: 1-888-849-3681 (TRS: 711)
- SEBB Members: 1-800-628-3481 (TRS: 711)

For more information:

- Refer to your plan's current certificate of coverage by visiting **Forms and publications at hca.wa.gov/ump-coc**
- Call ArrayRx at 1-888-361-1611 (TRS: 711)
Refer to the **UMP Preferred Drug List** by visiting hca.wa.gov/assets/pebb/ump-preferred-drug-list.pdf

November 01, 2025

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP053

Description

Pimavanserin (Nuplazid) is an orally administered atypical antipsychotic that works as a selective serotonin inverse agonist with an unknown mechanism of action.

Length of Authorization

- Initial: six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
pimavanserin (Nuplazid)	Parkinson's disease psychosis	34 mg capsules	30 capsules/30 days
		10 mg tablets	30 tablets/ 30 days

Initial Evaluation

- I. **Pimavanserin (Nuplazid)** may be considered medically necessary when the following criteria below are met:
 - A. Member is 18 years of age or older; **AND**
 - B. The medication is prescribed by or in consultation with a neurologist; **AND**
 - C. A diagnosis of **Parkinson's disease psychosis** with symptoms of hallucinations and delusions when the following are met:
 1. Symptoms of hallucinations and delusions have continued after reductions in current medications for Parkinson's disease or reductions in medications are not possible based on provider attestation; **AND**
 2. Treatment with clozapine or quetiapine has been ineffective or intolerable, unless both are contraindicated
- II. Pimavanserin (Nuplazid) is considered investigational when used for all other conditions, including but not limited to the diagnosis of:
 - A. Alzheimer's disease psychosis
 - B. Schizophrenia
 - C. Dementia related psychosis

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**

- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Member has experienced a reduction in delusions and hallucinations.

Supporting Evidence

- I. There is a lack of safety and efficacy in the use of pimavanserin (Nuplazid) for those under the age of 18.
- II. Due to the complexity around the diagnosis of Parkinson's disease (PD) and the treatment options, therapy should be prescribed by, or in consultation with, a neurologist.
- III. Psychosis is a frequent complication of PD, occurring in up to 40% of patients, particularly those in the advanced stages of the disease due to the adverse effects of antiparkinsonian medications over time; mainly, the dopamine agonists. There is a recommended algorithm by the Movement Disorder Society to approaching treatment in these patients. Firstly, ruling out if psychosis is from an underlying infection, and then assessing if the patient's psychosis is bothersome enough to warrant treatment. Treatment first begins with simply reducing or stopping PD medications if possible; if this is not possible or the symptoms continue, then initiating therapy with antipsychotic therapy (pimavanserin, quetiapine or clozapine) occurs.
- IV. Pimavanserin (Nuplazid) was studied in a 6-week, randomized, placebo-controlled, parallel-group study in 199 patients with a diagnosis (PD) and psychotic symptoms (hallucinations and/or delusions) severe and frequent enough to warrant antipsychotic treatment. Patients were all 40 years or older with a documented PD history of at least one year; the majority of patients were on PD medications at the study start and were on stable doses at least 30 days prior to the start of the study.
- V. The primary efficacy outcome was the change from baseline to week 6 in a PD-adapted scale for the assessment of positive symptoms (SAPS-PD). SAPS-PD is a 9-item scale adapted for PD from the Hallucinations and Delusions domains of the SAPS scale for schizophrenia. The SAPS-PD total score can range from 0 to 45 with higher scores reflecting greater severity of illness. A negative change in score indicates improvement.
- VI. A positive effect was seen on both hallucination and delusion components of the SAPS-PD for pimavanserin (n=95) versus placebo (n=90) [-3.06 (95% CI -4.91, -1.2)]. No difference in motor function was observed between pimavanserin and placebo. Although statistically significant, the clinical relevance of this result is unclear.
- VII. Pimavanserin (Nuplazid) also had an open-label extension (OLE) for patients completing one of the three double-blind, placebo-controlled studies. All patients received pimavanserin 34mg once daily for an additional four weeks of treatment. Efficacy results once again looked at SAPS-PD. Of 459 patients able to start the OLE, 424 patients continued in the trial for the four additional weeks. The SAPS-PD continued to show improvement during this four-week period, and those who originally were on placebo and switched over to pimavanserin showed the most positive effects during the OLE, having mean scores improving to the same level as the study arm group receiving pimavanserin during the double-blind trial.
- VIII. In 2022, a long-term outcomes review was reported for pimavanserin for psychosis in clinical practice. A retrospective chart review was conducted at the Movement Disorders practice in

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Providence, Rhode Island between 2016-2021 where 53 patients were identified as initiating pimavanserin, 45 of these patients had PD, and patients were on pimavanserin an average of 26 weeks. Initial improvement was seen in 47% of the group (25 of 53 patients). Due to inadequate control of symptoms with pimavanserin, an addition of another antipsychotic was needed to maintain a positive response for 10 of those 25 patients; whereas eight of the 25 patients were able to continue on pimavanserin for monotherapy.

- IX. There are not head-to-head trials of the antipsychotic agents used in PD psychosis. Multiple systemic reviews and meta-analyses have been completed to address this. One in 2023, reviewed 19 studies evaluating atypical antipsychotics in a total of 1,242 patients with PD psychosis. Based on the Clinical Global Impression Scale for Severity, pimavanserin with a standardized mean difference (SMD) of -4.81 (95% CI -5.39,-4.24) and clozapine with a SMD of -4.25 (95% CI, -5.24, -3.26) both significantly improved symptoms compared to placebo.
- X. The 2019 American Geriatrics Society Beers Panel recommends to generally avoid all antipsychotic medications in older patients with PD, with exceptions made for quetiapine, clozapine, and pimavanserin. The Movement Disorder Society rated clozapine as more efficacious compared to quetiapine, which was deemed to have insufficient evidence, and does not make any recommendation on pimavanserin (Nuplazid). An update was added one year later in 2019, discussing change in practice implications to the data on quetiapine, noting it was similarly efficacious to clozapine in a clozapine-controlled trial which did not have a placebo arm; updating quetiapine to possibly useful in PD-psychosis. There were no new comments to clozapine or pimavanserin regarding favoring one or the other.

Investigational or Not Medically Necessary Uses

- I. Pimavanserin (Nuplazid) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Alzheimer's disease psychosis
 - i. The use in AD psychosis remains experimental at this time. In August of 2022, the FDA issued a complete response letter noting it could not approve the new indication at this time and recommended an additional trial in this space.
 - B. Schizophrenia
 - i. The use of pimavanserin in schizophrenia remains experimental at this time while a phase III trial continues.
 - C. Dementia related psychosis
 - i. A complete response letter was issued in April 2021 that "cited a lack of statistical significance in some of the subgroups of dementia and insufficient numbers of patients with certain less common dementia subtypes as lack of substantial evidence of effectiveness to support approval."

References

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
istradefylline_Nourianz	Parkinson's Disease
levodopa_Inbrija	
apomorphine_Apokyn_Kynmobi	

Policy Implementation/Update:

Action and Summary of Changes	Date
Annual review; reformatted indication table, added in related policies, general formatting updates. Updated policy requirements to align with updated guidelines, addition of option to trial quetiapine OR clozapine. Updated supporting evidence to strengthen policy requirements.	11/2023
Transition from criteria to policy: Included requirements to attempt dose reduction in Parkinson's medications and specified what members must try and fail.	9/2019

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP225

Split Fill Management*

Description

Ponatinib (Iclusig) is an orally administered tyrosine kinase inhibitor with activity against unmutated and mutated BCR-ABL including the threonine-to-isoleucine mutation at position 315 (T315I).

Length of Authorization

- Initial: six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication*	Quantity Limit
ponatinib (Iclusig)	10 mg tablet	CP-CML with resistance or intolerance to two prior kinase inhibitors	30 tablets/30 days
	15 mg tablet	AP-CML, BP-CML, and Ph+ ALL for whom no other kinase inhibitors are indicated	30 tablets/30 days
	30 mg tablet	T315I-positive CML (any phase) or T315I-positive Ph+ ALL	30 tablets/30 days
	45 mg tablet	Newly diagnosed Ph+ ALL in combination with chemotherapy	30 tablets/30 days

*CML = chronic myeloid leukemia, CP = chronic phase, AP = accelerated phase, BP = blast phase, Ph+ = Philadelphia chromosome positive, ALL = acute lymphoblastic leukemia

Initial Evaluation

- I. **Ponatinib (Iclusig)** may be considered medically necessary when the following criteria are met:
 - A. Member is 18 years of age or older; **AND**
 - B. Medication is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
 - C. A diagnosis of one of the following:
 1. **Chronic Phase-Chronic Myeloid Leukemia (CP-CML); AND**
 - i. Documented resistance, or intolerance to, two prior tyrosine kinase inhibitors (TKIs) (e.g., dasatinib (Sprycel), imatinib (Gleevec), nilotinib (Tasigna), bosutinib (Bosulif); **OR**
 - a. Documented positive T315I mutation; **AND**
 - ii. Medication will not be used in combination with any other oncology therapy; **OR**

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2. **Accelerated Phase- Chronic Myeloid Leukemia (AP-CML), Blast Phase- Chronic Myeloid Leukemia (BP-CML), or Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia (Ph+ ALL); AND**
 - i. Provider attestation that all other tyrosine kinase inhibitors (TKIs) (e.g., dasatinib (Sprycel), imatinib (Gleevec), nilotinib (Tasigna), bosutinib (Bosulif) used to treat Accelerated Phase- Chronic Myeloid Leukemia (AP-CML), Blast Phase- Chronic Myeloid Leukemia (BP-CML), or Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia (Ph+ALL) have been ineffective, not tolerated, contraindicated or not indicated; **OR**
 - a. Documented positive T315I mutation; **AND**
 - ii. Medication will not be used in combination with any other oncology therapy; **OR**
3. **Newly diagnosed Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia (Ph+ ALL); AND**
 - i. Medication will be used in combination with chemotherapy (e.g., vincristine, cytarabine, methotrexate, cyclophosphamide, doxorubicin, daunorubicin, etc.)

- I. Ponatinib (Iclusig) is considered investigational when used for all other conditions, including but not limited to:
 - A. Newly diagnosed chronic phase chronic myeloid leukemia (CP-CML)

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If this applies, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Medication will not be used with any other oncology therapy; **OR**
 - Medication will be used in combination with chemotherapy (e.g., vincristine, cytarabine, methotrexate, cyclophosphamide, doxorubicin, daunorubicin, etc.) in newly diagnosed Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia (Ph+ ALL); **AND**
- IV. Member has exhibited response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread.

Supporting Evidence

- I. Ponatinib (Iclusig) is an oral tyrosine kinase inhibitor with activity against unmutated and mutated BCR-ABL, including the threonine-to-isoleucine mutation at position 315 (T315I), which is present in around 20% of patients with tyrosine kinase inhibitor-resistant disease.
- II. Ponatinib (Iclusig) carries four FDA approved indications and is used in the treatment of patients with chronic phase (CP) chronic myeloid leukemia (CML) with resistance or intolerance to at least two prior kinase inhibitors, accelerated phase (AP) or blast phase (BP) CML, Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) for whom no other kinase

inhibitors are indicated, T315I-positive CML (chronic phase, accelerated phase, or blast phase) or T315I-positive Ph+ ALL, and newly diagnosed Ph+ ALL in combination with chemotherapy.

Chronic Myeloid Leukemia (CML) and Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL) Resistant or Intolerant to Prior TKI

- III. The original FDA approval for ponatinib (Iclusig) took place in 2012 and was based on the PACE clinical trial which evaluated safety and efficacy of ponatinib (Iclusig). Post-marketing studies submitted to the FDA included a 5 year follow up PACE study and an ongoing OPTIC clinical trial, which informed of the optimal dosing in patients with CP-CML.
- IV. The PACE clinical trial was an open label, single arm, phase II study in adult subjects with CML (all phases) or Ph+ ALL with resistance/intolerance to dasatinib or nilotinib, or development of T315I mutation after tyrosine kinase inhibitor (TKI) therapy. There were 270 subjects in CP-CML, 85 subjects in AP-CML, 62 subjects in BP-CML, and 62 subjects in Ph+ALL. These subjects were further randomized based on T315I mutation status. Nearly one-third of subjects (29%) had the T315I mutation. The primary efficacy endpoint of major cytogenetic response (MCyR) by 12 months of treatment was met in 51% of those with resistance or intolerance to prior TKI therapy and in 70% of those with a positive T315I mutation status in the CP-CML cohort. In AP-CML, BP-CML, and Ph+ALL the primary endpoint was major hematologic response (MaHR) by 6 months of treatment which was met in 57% of those with prior resistance or intolerance to TKI therapy and in 50% of those with a positive T315I mutation status in the AP-CML cohort. MaHR was met in 35% of those with resistance or intolerance to prior TKI therapy and in 33% of those with a positive T315I mutation status in the BP-CML/Ph+ALL cohort.
- V. The five-year follow up study of ponatinib (Iclusig) demonstrated a continued clinical benefit in patients with heavily treated CML or Ph+ALL. The types of adverse events reported were generally similar to those reported previously and included rash (47%), abdominal pain (46%), thrombocytopenia (46%), headache (43%), and constipation (41%). Dose related adverse events included cardiovascular, cerebrovascular, and peripheral vascular events. The cumulative incidence of arterial occlusive events (AOEs) was 25% in the overall population (serious AOE, 20%) and 31% in the CP-CML population (serious AOE, 26%); higher cumulative incidence in CP-CML correlates with the longer duration of treatment.
- VI. OPTIC is an ongoing phase 2, open label, randomized, multicenter clinical trial evaluating response-based dosing regimens of ponatinib (Iclusig) with the aim of optimizing its efficacy and safety in patients with CP-CML who are resistant or intolerant to prior TKI therapy. Interim results at 21 months of follow up show benefit of ponatinib (Iclusig) in all three dosing regimens studied (15 mg, 30 mg, and 45 mg), with the 45 mg starting dose showing greatest efficacy results. Thus far, the FDA has made recommendations to start with the 45 mg dose which could subsequently be titrated down to 15 mg upon achievement of <1% BCR-ABL1. Primary analysis will provide a refined understanding of the benefit: risk profile of three different starting doses of ponatinib (Iclusig).

Newly Diagnosed Positive Acute Lymphoblastic Leukemia (Ph+ ALL)

- VII. The PhALLCON trial evaluated ponatinib in combination with reduced-intensity chemotherapy (n=154) in the treatment of newly diagnosed Ph+ ALL compared to imatinib with reduced-intensity chemotherapy (n=78) in a phase 3, open-label, global clinical trial randomized 2:1 (ponatinib: imatinib). Ponatinib was dosed 30 mg orally daily in combination with chemotherapy for 20 cycles. After completion of 20 cycles of chemotherapy, ponatinib monotherapy was continued at 30mg daily. Patients were able to decrease the dose to 15 mg orally daily based on MRD status after induction. Imatinib was dosed 600 mg orally daily for 20 cycles, followed by monotherapy thereafter. Patients did not have the option to reduce the dose of imatinib. The primary endpoint was MRD-negative complete remission at the end of induction (end of cycle

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3). This was defined as investigator-reported complete remission for 4 weeks or longer and MRD-negativity defined as $\leq 0.01\%$ BCR:ABL1/ABL1 molecular response (MR4). Ponatinib significantly achieved MRD-negative complete remission at the end of induction in 34.4% of patients compared to imatinib's 16.7% (risk difference, 0.18 [95% CI 0.06 – 0.29]; relative risk, 2.06 [95% CI 1.19 – 3.56]; p-value, 0.002). Secondary endpoints included event-free survival, progression-free survival, overall survival, MRD-negativity at the end of induction, and duration of MRD-negative complete remission. The only significant findings were progression-free survival (HR 0.58 [95% CI 0.41 – 0.83]) and those that achieved MRD-negativity at the end of induction (risk difference, 0.21 [95% CI 0.08 – 0.34]; relative risk, 1.94 [95% CI 1.19 – 3.17]; p-value, 0.002). The safety profiles for both ponatinib and imatinib were similar. The most common AEs experienced were ALT increase, hypertension, and decreased platelet, WBC, and neutrophils counts with 20 discontinuing ponatinib treatment and 10 discontinuing imatinib treatment due to adverse events. The adverse events weren't specified and overall, no deaths occurred due to treatment.

- VIII. For the treatment of Ph+ ALL, current NCCN guidelines recommend TKIs such as bosutinib (Bosulif), dasatinib (Sprycel), imatinib (Gleevec), nilotinib (Tasigna), or ponatinib (Iclusig) as preferred agents. Imatinib use in first line should be restricted to patients who cannot tolerate broader acting TKIs. Not all TKIs have been studied directly within the context of each regimen proposed by NCCN. There is limited data for bosutinib (Bosulif) in Ph+ ALL. Moreover, certain TKIs are contraindicated with specific BCR-ABL1 mutations; ponatinib (Iclusig) is the only TKI without any contraindicated mutations.
- IX. For the treatment of CP-CML, current NCCN guidelines recommend the following agents depending on the patient's risk score and mutation profile: imatinib (Gleevec), bosutinib (Bosulif), dasatinib (Sprycel), nilotinib (Tasigna) when there's resistance to two prior TKIs (category 2a). For the treatment of AP-CML and BP-CML, preferred regimens include bosutinib (Bosulif), dasatinib (Sprycel), nilotinib (Tasigna), or ponatinib (Iclusig). These agents are preferred over imatinib (Gleevec). Imatinib (Gleevec) may be considered in patients with contraindications to other TKIs.

Investigational or Not Medically Necessary Uses

- I. Ponatinib (Iclusig) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Newly diagnosed CP-CML
 - i. Ponatinib (Iclusig) was studied as a first line agent in patients newly diagnosed with CP-CML and showed an increase in risk of serious adverse reactions 2-fold compared to imatinib (Gleevec) 400 mg once daily. This prospective randomized clinical trial was subsequently halted for safety. Ponatinib (Iclusig) treated patients exhibited a greater incidence of myelosuppression, pancreatitis, hepatotoxicity, cardiac failure, hypertension, and skin and subcutaneous tissue disorders. Ponatinib (Iclusig) is not indicated and is not recommended for the treatment of patients with newly diagnosed CP-CML.

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side*

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effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
imatinib (Gleevec®)	Chronic eosinophilic leukemia
	Dermatofibrosarcoma protuberans, unresectable, recurrent, and/or metastatic
	Gastrointestinal stromal tumor, Kit (CD117)-positive, adjuvant treatment
	Gastrointestinal stromal tumor, Kit (CD117)-positive, unresectable or metastatic disease
	Hypereosinophilic syndrome
	Myelodysplastic syndrome, PDGFR gene rearrangement
	Myelodysplastic syndrome, chronic, PDGFR gene rearrangement
	Philadelphia chromosome-positive acute lymphoblastic leukemia, newly diagnosed, in combination with chemotherapy
	Philadelphia chromosome-positive acute lymphoblastic leukemia, relapsed/refractory
	Philadelphia chromosome positive chronic myelogenous leukemia, accelerated phase or blast crisis
	Philadelphia chromosome positive chronic myelogenous leukemia, chronic phase, after failure of interferon-alpha therapy
	Philadelphia chromosome positive chronic myelogenous leukemia, chronic phase, newly diagnosed
	Systemic mast cell disease, aggressive, D816V c-Kit mutation negative or unknown
dasatinib (SPRYCEL®)	Philadelphia chromosome-positive (Ph+) Chronic myeloid leukemia (CML)/ Ph+ Acute lymphoblastic leukemia (ALL)
	Chronic phase CML
	Gastrointestinal Stromal Tumors (GIST)
bosutinib (Bosulif®)	CML, newly diagnosed chronic phase
	CML, resistant or intolerant to prior therapy
nilotinib (Tasigna®; Danziten™)	Newly diagnosed OR resistant/intolerant Ph+ CML in chronic phase
	Newly diagnosed Ph+ CML in chronic phase
	Resistant or intolerant Ph+ CML Gastrointestinal Stromal Tumors (GIST)

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Policy Implementation/Update:

Action and Summary of Changes	Date
Updated initial approval period to 6 months. Updated policy criteria to reflect most up to date format. Added newly diagnosed Ph+ ALL indication with relevant supporting evidence. Added related policies table.	02/2025
Policy criteria transitioned to a new format; criteria changes include the removal of laboratory monitoring requirements (blood counts, hepatic enzyme tests, serum lipase) and monitoring of atrial thrombotic events, addition of a new dosage forms 10 mg and 30 mg tablets, and addition of requiring two prior TKIs in CP-CML, consistent with the FDA labeling change.	03/2021
Policy criteria created	05/2013

Policy Type: PA

Pharmacy Coverage Policy: UMP283

Description

Prescription digital therapeutics (PDTs) are devices, internet applications or other software-based technology intended for the prevention, management, or treatment of a medical condition. PDTs are cleared, authorized, or approved under section 510(k), 513(f)(22), or 515 of the federal food, drug, and cosmetic act, and must be prescribed by a licensed healthcare provider. The purpose of this policy is to ensure the appropriate use of these interventions.

Length of Authorization

- Initial:
 - i. Somryst: one time authorization to cover up to 9-week treatment
 - ii. EndeavorRx: NA
- Renewal:
 - i. Somryst: not applicable; this is a single one-time treatment
 - ii. EndeavorRx: NA

Prescription Digital Therapeutics (PDTs) included in this Policy

Product Name	Indication	Quantity Limit
Somryst*	Chronic Insomnia	1 x access, up to 9-week treatment
EndeavorRx	Attention Deficit and Hyperactivity Disorder (ADHD)	One activation code/30 days

* Somryst NDC 96439-0030-01

Initial Evaluation

- I. **Somryst (digital therapy)** may be considered medically necessary when the following criteria are met:
 - A. Member is 22 years of age or older; **AND**
 - B. A diagnosis of **chronic insomnia**; **AND**
 1. Attestation by provider that all the following are met:
 - i. Member is under their supervision; **AND**
 - ii. Member is able to read and understand English; **AND**
 - iii. Member is familiar with how to use mobile apps; **AND**
 2. Attestation by provider member's daily life or work does not require them to be highly alert or cautious (e.g., long-haul truck drivers, long-distance bus drivers, air traffic controllers, operators of heavy machinery, certain assembly line jobs)
- II. **EndeavorRx** is not covered by the pharmacy benefit.

- I. Somryst and EndeavorRx are considered investigational when used for all other conditions, including but not limited to:
 - A. Short-term insomnia
 - B. Parasomnia
 - C. When used as a stand-alone therapy
 - D. Cognitive function improvement in disease conditions other than ADHD (e.g., autism spectrum disorder, systemic lupus erythematosus [SLE])
 - E. Sensory processing disorder

Renewal Evaluation

- I. Somryst:
 - A. Not applicable. Somryst is a one-time 9-week treatment.
- II. EndeavorRx:
 - A. Not applicable. EndeavorRx is not covered by the pharmacy benefit.

Supporting Evidence

Somryst:

- I. The American Academy of Sleep Medicine (AASM) strongly recommends cognitive behavioral therapy for insomnia (CBT-I) as part of the initial recommended approaches to treat chronic insomnia in adults.
 - CBT-I combines one or more cognitive therapies, alongside education about sleep regulation, stimulus control, and sleep restriction therapy. This can also include sleep hygiene education, relaxation training, and use of sleep diaries.
 - CBT-I is digitally delivered via the Somryst app on a tablet or smartphone.
- II. While cognitive behavioral therapy is the standard of care in the treatment of insomnia, the FDA authorization of Somryst was based on a controlled study where CBT-I was delivered by a computer. Thirty-four subjects were randomized to receive either control (sleep diary) or computer-based CBT-I. The CBT-I treatment group had a statistically significant difference in improved sleep versus control.
- III. Somryst is indicated in patients 22 years of age and older with chronic insomnia. Product claim includes improving insomnia symptoms.
- IV. Somryst use is intended as a single 9-week treatment, under the supervision of a provider.
- V. Somryst guides the user through various activities and modules over 6 to 9 weeks; there is no data to support repeat use or use beyond this time.
- VI. Since CBT-I is delivered via a digital means on a tablet or smartphone, safe and typical use requires familiarity with apps and ability to read and understand English.
- VII. Treatment with Somryst includes both sleep restriction and consolidation which can cause sleepiness, especially in the early stages of using this prescribed digital therapeutic. For individuals who must be alert or cautious to avoid serious accidents in their job or daily life, Somryst should not be used. Examples include: long-haul truck drivers, long-distance bus drivers, air traffic controllers, those who operate heavy machinery or select assembly line work.

EndeavorRx:

- VIII. EndeavorRx (Akili Interactive Labs, Inc.) is an FDA-authorized Prescription Digital Therapeutic (PDT) indicated to improve attention function in children eight to 12 years of age with attention-

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deficit hyperactivity disorder (ADHD). Delivered via an action video game experience, one prescription of EndeavorRx provides 30 days of access and is administered daily (25 minutes, five days/ week).

- IX. Utility of EndeavorRx has been assessed in the improvement of attention function as measured by computer-based testing in children ages eight to 12 years old with primarily inattentive or combined-type ADHD, who have a demonstrated attention issue. During clinical trials, patients who engaged with EndeavorRx demonstrated improvements in a digitally assessed measure, (Test of Variables of Attention [TOVA]), of sustained and selective attention. Patients using EndeavorRx may not display benefits in typical behavioral symptoms, such as hyperactivity. EndeavorRx should be considered for use as part of a therapeutic program that may include clinician-directed therapy, medication, and/or educational programs, which further address symptoms of the disorder.
- X. Although there are no contraindications noted to the use of EndeavorRx, this PDT may not be appropriate for patients with photo-sensitive epilepsy, color blindness, or physical limitations that restrict the use of a mobile device.
- XI. Treatment recommendations for patients with ADHD vary based on age and include behavioral changes, cognitive therapy, and pharmacotherapy. Pharmacotherapy options include stimulants (e.g., methylphenidate and amphetamines) and non-stimulants (e.g., guanfacine, atomoxetine). The American Academy of Pediatrics (AAP) ADHD guidelines recommend parent training in behavior management (PTBM) and behavioral classroom interventions as the first-line treatment for children under 12 years of age. Additionally, for children six years and above, the addition of pharmacotherapy may be considered.
- XII. EndeavorRx is the first PDT for the treatment of ADHD in children and was FDA-authorized via a *de novo* pathway. It may be considered an adjunct therapy combined with PTBM, clinician-directed behavioral therapy, and pharmacotherapy. EndeavorRx is not recommended to be used as a stand-alone therapy or as a substitute for pharmacotherapy. As of June 2023, The AAP guideline has not been updated to include EndeavorRx as a treatment option for ADHD.
- XIII. EndeavorRx was assessed via two clinical trials, STARS-ADHD, a phase 3, randomized (1:1), double-blind clinical trial, which assessed response to EndeavorRx versus a digital sham control; and STARS-ADJUNCT, an open-label, dual-cohort trial which assessed EndeavorRx as an adjunct to stimulant therapy. STARS-ADHD included patients (N=348) aged eight to 12 years with baseline ADHD rating scale score (ADHD-RS-IV) ≥ 28 , and Test of Variables of Attention - Attentional Performance Index (TOVA-API) ≤ -1.8 . Mean change in TOVA-API from baseline to day 28 was assessed as the primary outcome. STARS-ADJUNCT trial included patients (N= 236), eight to 14 years of age who were assigned to an on-stimulant cohort (n= 130) or a non-stimulant cohort (n=76). All patients had ADHD impairment rating score (ADHD-IRS) ≥ 3 . Mean change in ADHD-IRS from baseline to day 28 was the primary outcome. A 28-day treatment during STARS-ADHD led to statistically significant improvement in TOVA-API for the trial participants with a positive TOVA-API score 0.9 points higher in the treatment arm versus digital control ($p=0.0060$). STARS-ADJUNCT trial measured ADHD-IRS mean change from baseline to day 28, which reported a reduction of -0.7 (95% CI, $-0.86, -0.50$; $p < 0.001$) in the on-stimulant cohort, and -0.5 (95% CI, $-0.73, -0.32$; $p < 0.001$) in the non-stimulant cohort.
- XIV. During STARS-ADJUNCT, exploratory secondary outcomes at day 84 (after a 28-day treatment pause), reported incremental improvement in ADHD-IRS (68.3%), $\geq 30\%$ improvement in ADHD-RS (45.3%), and CGI-I scores ≤ 2 (27.6%) across both cohorts. Investigator-monitored compliance

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- rates were 83% and 81% for STARS-ADHD and STARS-ADJUNCT trials, respectively. Additionally, both clinical trials reported patient-reported improvement in attention deficit (75%).
- XV. Limitations of the clinical program for EndeavorRx include a narrow population age, exclusion of patients with psychiatric comorbidities, and short duration of intervention. However, both clinical trials reported consistent, statistically significant improvement in ADHD-related impairment and symptoms of inattention. TOVA-API is a validated tool of improvement in attention deficit and inhibitory control. Clinically meaningful improvements after three months therapy during STARS-ADJUNCT trial (ADHD-RS and CGI-I scores) provide additional indicators of efficacy. For the majority of pediatric patients with ADHD, when used as an adjunct therapy, EndeavorRx may serve as a practical intervention. Overall quality of evidence is considered low to moderate.
 - XVI. Overall, 12 (7%) and 37 (18%) participants experienced intervention-related adverse reactions (IRAEs) during STARS-ADHD and STARS-ADJUNCT, respectively. During STARS-ADHD, the most common IRAEs between the intervention versus digital control arms respectively, were decreased frustration tolerance (3% vs 0%), headache (2% vs 1%), and irritability (1% in each arm). For STARS-ADJUNCT, IRAEs were evenly distributed between the on-stimulants and non-stimulants cohorts, and included decreased frustration tolerance (13%), irritability (1.5%), headache (1.9%), and dizziness (1%). There were no serious adverse reactions reported. Three participants discontinued STARS-ADJUNCT due to IRAEs. Current safety data for EndeavorRx is limited to the clinical trial population and the real-world long-term safety remains unknown.

Investigational or Not Medically Necessary Uses

- I. Somryst and EndeavorRx have not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Short-term insomnia
 - B. Parasomnia
 - C. When used as a stand-alone therapy
 - D. Cognitive function improvement in disease conditions other than ADHD (e.g., autism spectrum disorder, systemic lupus erythematosus (SLE))
 - E. Sensory processing disorder
- II. EndeavorRx has been assessed in clinical trials for pediatric patients with ADHD and comorbid sensory processing disorder (SPD) as well as autism spectrum disorder (ASD). Results of these clinical trials are not available as of June 2023. EndeavorRx has not received FDA-authorization for the above indications.
- III. Additional clinical trial to assess the safety and efficacy of EndeavorRx in adolescent population (12 to 17 years of age) with ADHD is ongoing. In June 2023, EndeavorOTC, a non-prescription version of EndeavorRx, became available for use by adults (>18 years of age). EndeavorOTC is available as a downloadable software application (App) compatible with leading cellular phone operating systems and requires a monthly subscription fee. As of June 2023, the results of the clinical trial of EndeavorRx in the adult population are not available. Over-the-counter (OTC) devices and digital therapeutics may be considered excluded in accordance with the benefit designs for this health plan.

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1. Somryst [Clinician Information]. Boston, MA: Pear Therapeutics, Inc. March 2020.

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3. Edinger JD, Arnedt JT, Bertisch SM, et al. Behavioral and psychological treatments for chronic insomnia disorder in adults: an American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med*. 2021;17(2):255–262
4. Kollins SH, DeLoss DJ, Cañadas E, Lutz J, et al.. A novel digital intervention for actively reducing severity of paediatric ADHD (STARS-ADHD): a randomised controlled trial. *Lancet Digit Health*. 2020 Apr;2(4):e168-e178.
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Related Policies

Currently there are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy updated to remove EndeavorRx as a covered benefit	12/2023
Policy created (EndeavorRx) and combined with Somryst to create a Prescription Digital Therapeutics policy.	08/2023

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP080

Description

Pretomanid is an orally administered nitroimidazooxazines antimycobacterial agent.

Length of Authorization

- Initial: six months
- Renewal: N/A

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit	DDID
pretomanid	200 mg tablet	Pulmonary tuberculosis that is extensively drug resistant (XDR), treatment intolerant, or nonresponsive multi-drug resistant (MDR)	30 tablets/30 days	TBD

Initial Evaluation

- I. Pretomanid may be considered medically necessary when the following criteria below are met:
 - A. The member is 18 years of age or older; **AND**
 - B. The medication is prescribed by, or in consultation with a pulmonologist or infectious disease specialist; **AND**
 - C. A diagnosis of **pulmonary extensively drug resistant (XDR), treatment-intolerant, or nonresponsive multidrug-resistant (MDR) tuberculosis (TB)** when the following are met:
 1. Documentation of resistance to isoniazid, rifamycins, a fluoroquinolone and an injectable antimicrobial (e.g., amikacin, kanamycin, or capreomycin); **AND**
 2. Documentation of intolerance to para-aminosalicylic acid (PAS), ethionamide, aminoglycosides or fluoroquinolones; **AND**
 3. The member will be using pretomanid in combination with bedaquiline (Situro) **AND** linezolid (Zyvox) for the duration of therapy; **AND**
 4. The member will have directly observed treatment (DOT) plan in place
- II. Pretomanid is considered investigational when used for all other conditions, including but not limited to:
 - A. The use of pretomanid in combination with drugs other than bedaquiline (Situro) and linezolid (Zyvox)
 - B. Drug-sensitive (DS) tuberculosis
 - C. Latent infection due to Mycobacterium tuberculosis
 - D. Extra-pulmonary infection due to Mycobacterium tuberculosis

- E. Multidrug-resistant tuberculosis that is not treatment-intolerant or nonresponsive to standard therapy

Supporting Evidence

- I. Pretomanid was studied in a Phase 3, open-label trial with 109 adult patients with pulmonary TB that are XDR, treatment intolerant, or non-responsive MDR. In that trial, the safety and efficacy of pretomanid in combination with bedaquiline and linezolid was assessed.

Definition of TB Types	
Drug-resistant TB	TB caused by an isolate of <i>Mycobacterium tuberculosis</i> (M. tuberculosis) that is resistant to one or more antituberculous drugs
Multidrug-resistant TB (MDR-TB)	TB caused by an isolate of M. tuberculosis that is resistant to both isoniazid (INH) and rifampin and possibly additional agents
Extensively drug-resistant TB (XDR-TB)	TB caused by an isolate of M. tuberculosis that is resistant to at least INH, rifampin, and fluoroquinolones as well as either aminoglycosides (e.g. amikacin, kanamycin) or capreomycin or both
Totally drug-resistant TB (TDR-TB)	TB caused by an isolate of M. tuberculosis resistant to all locally tested medications

- II. The primary efficacy outcome was the incidence of bacteriologic failure, relapse, or clinical failure through follow up until six months after the end of treatment; of the 107 patients assessed, 12 (11%) patients were classified as treatment failure, while 95 (89%) patients were classified as treatment success. Treatment success was defined as culture negative status at six months post treatment.
- III. No pediatric patients were included in the trial.
- IV. Pretomanid was only studied in combination with bedaquiline (Situro) and linezolid (Zyvox).
- V. Patients that were included in the trial demonstrated resistance to isoniazid, rifamycins, a fluoroquinolone and an injectable antimicrobial, and had intolerance to para-aminosalicylic acid (PAS), ethionamide, aminoglycosides or fluoroquinolones.

Investigational or Not Medically Necessary Uses

- I. Safety and efficacy has not been established for the use of pretomanid in combination with drugs other than bedaquiline (Situro) and linezolid (Zyvox).
- II. Pretomanid was FDA-approved on an accelerated approval pathway under the Limited Population Pathway for Antibacterial and Antifungal Drugs. As stated in the label, the approval of this indication is based on limited clinical safety and efficacy data. Therefore, the use of this drug is indicated for a very specific population of patients, and antimicrobial stewardship practices should be applied when treating this population of patients. Therefore, the use of pretomanid in setting

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other than the label indication [pulmonary extensively drug resistant (XDR), treatment-intolerant, or nonresponsive multidrug-resistant (MDR) tuberculosis (TB)], is considered experimental and investigational.

References

1. Pretomanid [Prescribing Information]. Mylan: Hyderabad, India. August 2019.
2. Sirturo [Prescribing information]. Janssen Therapeutics: Titusville, NJ. December 2012.
3. Center for Disease Control and Prevention: Provisional CDC Guidelines for the Use and Safety Monitoring of Bedaquiline Fumarate (Sirturo) for the Treatment of Multidrug-Resistant Tuberculosis. Available at: https://www.cdc.gov/mmwr/preview/mmwrhtml/rr6209a1.htm?s_cid=rr6209a1_e
4. World Health Organization: WHO Guidelines on Tuberculosis. Available at: <https://www.who.int/news-room/fact-sheets/detail/tuberculosis>
5. The Food and Drug Administration: FDA Briefing Document on Pretomanid 200 mg Tablet. Meeting of the Antimicrobial Drugs Advisory Committee (AMDAC). June 2019.
6. Clinicaltrial.gov

Policy Implementation/Update:

Date Created	September 2019
Date Effective	November 2019
Last Updated	
Last Reviewed	

Action and Summary of Changes	Date

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Policy Type: PA

Pharmacy Coverage Policy: UMP044

Description

Glycopyrronium (Qbrexza) is a topically administered anticholinergic cloth that works to reduce acetylcholine on sweat glands. Sofpironium (Sofdra) is a topically administered anticholinergic gel that inhibits the action of M3 acetylcholine receptors on sweat gland.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
glycopyrronium (Qbrexza)	Primary axillary hyperhidrosis	Topical 2.4% single-use pre-moistened cloth	30 cloths/30 days
sofpironium (Sofdra)		12.45% topical gel	40.2 mL/30 days

Initial Evaluation

- I. **Glycopyrronium (Qbrexza) and sofpironium (Sofdra)** may be considered medically necessary when the following criteria are met:
 - A. Member is nine years of age or older; **AND**
 - B. Member has a diagnosis of **primary axillary hyperhidrosis** when the following are met:
 1. Severe symptoms of axillary hyperhidrosis (e.g., sweating most of the time or all of the time, sweating that is unmanageable, severe or very severe sweating for no apparent reason); **AND**
 2. Provider attestation that secondary axillary hyperhidrosis has been ruled out; **AND**
 - C. Member has a history of medical complications such as skin infections requiring treatment; **OR**
 1. Member has significant impacts on activities of daily living due to the condition (e.g., constant patterns of impairment in work or school performance, isolated lifestyle, frequent change in clothing, difficulty in relationships, social gatherings and/or activities, etc.); **AND**
 - D. Medication is not used in combination with other anticholinergic products for the treatment of primary axillary hyperhidrosis (e.g., glycopyrronium (Qbrexza) cloth, Botulinum toxin, oxybutynin, glycopyrrolate); **AND**
 - E. Treatment with prescription-strength aluminum chloride hexahydrate 20% (Drysol) solution has been ineffective, not tolerated, or is contraindicated.
- II. Glycopyrronium (Qbrexza) and sofpironium (Sofdra) may be considered investigational when used for all other conditions, including but not limited to:

- A. Treatment of palmar hyperhidrosis
- B. Treatment of amputation site hyperhidrosis
- C. Treatment of hyperhidrosis in pediatric patients less than nine years of age

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Member has exhibited reduction in spontaneous axillary sweat production and improvement or stability of disease symptoms (i.e., improvement in work performance/productivity, change of clothing, relationships, social gatherings, and/or activities, etc.)
- IV. Medication is not used in combination with other anticholinergic products for the treatment of primary axillary hyperhidrosis (e.g., glycopyrronium (Qbrexza) cloth, Botulinum toxin, oxybutynin, glycopyrrolate)

Supporting Evidence

- I. Glycopyrronium (Qbrexza) and sofipirionium (Sofdra) are aluminum-free topical anticholinergic agents FDA approved for the treatment of primary axillary hyperhidrosis in patients aged nine years and older. CARDIGAN 1 and CARDIGAN 2 trials did not study sofipirionium (Sofdra) in patients less than nine years of age, thus there's no established efficacy and safety supporting the use of sofipirionium (Sofdra) in this population. The FDA considered the approval age starting at nine years old because puberty starts as early as nine years old making these patients susceptible to primary axillary hyperhidrosis.
- II. The ATMOS-1 and ATMOS-2 trials which led to the FDA-approval of glycopyrronium (Qbrexza) included patients with a Hyperhidrosis Disease Severity Scale (HDSS) grade of three or greater, defined by barely tolerable or intolerable sweating and frequent or consistent interference with daily activities. The scoring scale used in sofipirionium (Sofdra)'s clinical trial program was the Hyperhidrosis Disease Severity Measure-Axillary (HDSM-Ax-7). Patients were included if they had a score of three or greater corresponding to severe or very severe axillary hyperhidrosis. Although not used in clinical practice, these scoring scales are validated and can translate to excessive sweating that significantly impacts patient's ability to perform activities of daily living. This is an important factor to consider because it can negatively affect patients' physical wellbeing and overall quality of life. Efficacy of glycopyrronium (Qbrexza) and sofipirionium (Sofdra) in less severe disease is not well defined.
- III. Glycopyrronium (Qbrexza) and sofipirionium (Sofdra) are FDA approved in the setting of primary axillary hyperhidrosis. To make an accurate diagnosis, secondary causes of hyperhidrosis should be ruled out. Causes of secondary hyperhidrosis include, but are not limited to, alcohol use, endocrine/metabolic disorders, febrile illness/infection, malignancies, neurologic disorders, psychiatric disorders, menopause, and medications. Patients with generalized, secondary hyperhidrosis usually present as adults and report sweating that occurs both while awake and asleep. Medications should be carefully reviewed, as the presentation and treatment approach

for secondary hyperhidrosis is different. According to the American Family Physician (AAFP), secondary hyperhidrosis is ruled out if there's focal and visible excessive sweating for longer than six months without an apparent cause. Additionally, patients must meet at least two of the following criteria: bilateral, symmetric sweating, impairment of daily activities, occurrence at least once per week, age of onset younger than 25 years, no occurrence during sleep, and positive family history. The 2018 International Hyperhidrosis Society (IHS) also recommends ruling out secondary hyperhidrosis and follows a similar approach.

- IV. Patients with axillary hyperhidrosis are at an increased risk for developing bacterial, fungal, and viral skin infections. Medical necessity for treatment with glycopyrronium (Qbrexza) and sofipironium (Sofdra) is established in those suffering from severe disease defined by past history of medical complications such as skin infections or having significant impact activities of daily living. In the absence of these manifestations of the disease, treatment is considered not medically necessary/cosmetic.
- V. Glycopyrronium (Qbrexza) was studied in two, Phase 3, randomized, double-blind, vehicle controlled, parallel group trials, ATMOS-1 (N=344) and ATMOS-2 (N=353) evaluating daily glycopyrronium (Qbrexza) application to each axilla over four weeks. The primary endpoint, Axillary Sweating Daily Diary (ASDD), is a questionnaire for axillary hyperhidrosis measuring presence, severity, and impact of bothersome of sweating. Glycopyrronium (Qbrexza) applied topically daily over four weeks reduced the severity of sweating and reduced sweat production. Additionally, patients who continued to use glycopyrronium (Qbrexza) every day beyond four weeks continued to produce less sweat throughout the 48-week study period.
 - ATMOS-1: 52.8% vs 28.3%; $P < 0.001$
 - ATMOS-2: 66.1% vs 26.9%; $P < 0.001$
- VI. Sofipironium (Sofdra) was studied in two Phase 3, multicenter, double-blinded, vehicle-controlled trials in patients with primary axillary hyperhidrosis. CARDIGAN 1 (N=350) and CARDIGAN 2 (N=351) evaluated the efficacy and safety of daily treatment of sofipironium (Sofdra) applied to each axilla compared to placebo-controlled arm over a six-week period. The co-primary endpoints of these trials were the proportion of patients having at least a 2-point improvement in the HDSM-Ax-7 scale score from baseline to end of treatment (EOT) day 43, and the change in GSP from baseline to EOT. Results in both CARDIGAN 1 and CARDIGAN 2 showed positive outcomes for sofipironium (Sofdra) arm compared to placebo. Both trials also showed statistical significance with clinically meaningful improvements in HDSM-Ax score and GSP.
 - CARDIGAN 1: 49% vs 29%; $P = 0.0005$
 - CARDIGAN 2: 64% vs 48%; $p = 0.004$
- VII. The most common adverse reactions occurring in more than $\geq 2\%$ of participants in glycopyrronium (Qbrexza) and sofipironium (Sofdra) trials are dry mouth, blurred vision, application site erythema, mydriasis, application site dermatitis, application site pruritic, urinary retention, and application site irritation.
- VIII. There are no studies studying glycopyrronium (Qbrexza) or sofipironium (Sofdra) in combination with other agents; thus, efficacy and safety of combination treatments have not been established. Glycopyrronium (Qbrexza) and sofipironium (Sofdra) should only be used as monotherapy.
- IX. The International Hyperhidrosis Society (IHS) guidelines (2018) recommend topical antiperspirants (aluminum and zirconium salts) or glycopyrronium (Qbrexza) cloths as first line

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therapy for the management of primary focal axillary hyperhidrosis. The typical approach to treatment starts with over-the-counter (OTC) antiperspirants, followed by clinical strength OTC antiperspirants and prescription strength antiperspirants that contain aluminum chloride hexahydrate as an active ingredient (e.g., Drysol). Treatment with prescription-strength aluminum chloride hexahydrate 20% (Drysol) is required prior to pursuing coverage for glycopyrronium (Qbrexza) and sofpironium (Sofdra) as it represents the next step in treatment for severe hyperhidrosis after OTCs and is a safe and cost-effective alternative to topical anticholinergics products. Additionally, the American Family Physician guidelines (2018) recommend topical 20% aluminum chloride (Drysol) as a first-line treatment in most cases of primary focal hyperhidrosis, regardless of severity and location. Oral anticholinergics, such as oxybutynin and glycopyrrolate, are used as refractory treatment options and can pose greater risk of generalized anticholinergic side effects due to higher systemic absorption compared to topical options. Additionally, oral anticholinergics pose a concern for overheating in a subset of patients at risk for this adverse event (e.g., those who work outside, athletes).

- X. After topical antiperspirants (aluminum and zirconium salts) or glycopyrronium (Qbrexza) cloths, the International Hyperhidrosis Society (IHS) guidelines (2018) recommend Botulinum ToxinA injections, or glycopyrronium (Qbrexza) cloths (if not used as first-line), or microwave thermolysis as second line therapies. Oral systemic medications such as anticholinergics, beta-blockers, and calcium-channel blockers are recommended in cases of unsatisfactory response to second line therapies. The last line of treatment includes local sweat gland ablation (e.g., curettage or liposuction) or endoscopic thoracic sympathectomy after topical and medical treatments have failed.

Investigational or Not Medically Necessary Uses

- I. Glycopyrronium (Qbrexza) and sofpironium (Sofdra) have not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Palmar hyperhidrosis
 - i. An open label extension cohort study (NCT04906655) evaluating the use of glycopyrronium (Qbrexza) in palmar hyperhidrosis has been completed as of May 2022. However, quality of evidence associated with this study is low due to lack of randomization and placebo control. The results also did not achieve minimally clinically important differences (MCID's). There is currently lack of sufficient evidence or additional scientific literature to support the use of glycopyrronium (Qbrexza) in patients with palmar hyperhidrosis.
 - ii. A multicenter, randomized, double blind, vehicle-controlled, Phase 2 study (NCT02682238) evaluating the safety and local tolerability of sofpironium bromide 15% gel for the use of palmar hyperhidrosis in 49 patients 18 years of age and older has been completed. The primary endpoint studied safety while the secondary endpoints looked at efficacy as determined by the Hyperhidrosis Disease Severity Scale (HDSS) and Gravimetrically Measured Sweat Production (GMSP). While the trial demonstrated that most adverse events were mild to moderate, efficacy data was not statistically evaluated. Longer-term, Phase 3, randomized clinical trials in a greater number of patients are needed to establish efficacy of sofpironium (Sofdra) in this population.

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B. Hyperhidrosis of amputation sites

- i. A prospective, double-blind, placebo-controlled, randomized, cross-over trial (NCT04924036) evaluating the use of glycopyrronium (Qbrexza) in hyperhidrosis of amputation sites has been completed as of May 2024; however, results have not been posted nor published for review. There is currently lack of sufficient evidence or additional scientific literature to support the use of glycopyrronium (Qbrexza) and sofipirionium (Sofdra) in patients with hyperhidrosis of amputation sites.

C. Hyperhidrosis in pediatric patients less than nine years of age

- i. There is lack of sufficient evidence and lack of ongoing or active trials studying the use of glycopyrronium (Qbrexza) or sofipirionium (Sofdra) in pediatric patients less than nine years of age.

References

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Related Policies

Currently there are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	11/2024

Policy Type: PA

Pharmacy Coverage Policy: UMP141

Description

Obeticholic acid (Ocaliva) is a Farnesoid X Receptor (FXR) agonist. Elafibranor (Iqirvo) is a dual PPAR-alpha and PPARδ agonist. Seladelpar (Livdelzi) is a selective PPARδ agonist.

Length of Authorization

- Initial:
 - **Obeticholic acid (Ocaliva):** six months
 - **All other agents:** 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
obeticholic acid (Ocaliva)	Primary Biliary Cholangitis (PBC)	5 mg tablets	30 tablets/30 days
		10 mg tablets	
elafibranor (Iqirvo)		80 mg tablets	30 tablets/30 days
seladelpar (Livdelzi)		10 mg capsules	30 capsules/30 days

Initial Evaluation

- I. **Obeticholic acid (Ocaliva), Elafibranor (Iqirvo), or seladelpar (Livdelzi)** may be considered medically necessary when the following criteria below are met:
 - A. Member is 18 years of age or older; **AND**
 - B. Medication is prescribed by, or in consultation with, a gastroenterologist or hepatologist; **AND**
 - C. Must not be used in combination with another primary biliary cholangitis (PBC) drug (e.g., obeticholic acid (Ocaliva), elafibranor (Iqirvo), or seladelpar (Livdelzi)); **AND**
 - D. A diagnosis of **Primary Biliary Cholangitis (PBC)** (i.e., primary biliary cirrhosis); **AND**
 1. Diagnosis confirmed by two of the following:
 - i. Alkaline phosphatase (ALP) level at least 1.67 times the upper limit of normal (ULN, normal range: 44-147 IU/L)
 - ii. Positive antimitochondrial antibodies (AMA) test or other PBC-specific autoantibodies, (including sp100 or gp210), if AMA is negative
 - iii. Histopathologic evidence seen on biopsy (i.e., nonsuppurative cholangitis and destruction of small or medium-sized bile ducts); **AND**
 - E. The member did not have an adequate biochemical response after treatment with a maximally tolerated dose of ursodiol for at least 6 months (defined as an alkaline phosphatase (ALP) level less than or equal to 1.67 times the ULN (44-147 IU/L) or a total bilirubin less than the ULN (1 mg/dL); **AND**
 - F. Will be used in combination with ursodiol; **OR**
 1. Treatment with ursodiol was not tolerated; **AND**

- G. Member does not have decompensated liver disease (e.g. ascites, variceal bleeding, hepatic encephalopathy)
- II. Elafibranor (Iqirvo), seladelpar (Livdelzi), and obeticholic acid (Ocaliva) are considered investigational when used for all other conditions, including but not limited to:
 - A. Metabolic Dysfunction-Associated Steatohepatitis (MASH)/Non-alcoholic steatohepatitis (NASH)
 - B. Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)/Non-alcoholic fatty liver disease (NAFLD)
 - C. Familial partial lipodystrophy
 - D. Obesity
 - E. Digestive system disease/symptoms (bile acid diarrhea, unspecified diarrhea, gallstones, primary sclerosing cholangitis, biliary atresia, etc.)

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Medication will not be used in combination with another primary biliary cholangitis (PBC) drug (e.g., elafibranor (Iqirvo), seladelpar (Livdelzi), or obeticholic acid (Ocaliva)); **AND**
- IV. Member has a diagnosis of **Primary Biliary Cholangitis (PBC)** (i.e., primary biliary cirrhosis); **AND**
 - A. Member does not have decompensated liver disease (e.g., ascites, variceal bleeding, hepatic encephalopathy); **AND**
- V. Member has exhibited improvement or stability of disease symptoms (e.g., reduction of pruritus, reduced fatigue, or decrease in alkaline phosphate levels)

Supporting Evidence

- I. Obeticholic acid (Ocaliva) is a Farnesoid X Receptor (FXR) agonist and elafibranor (Iqirvo) and seladelpar (Livdelzi) are peroxisome proliferator-activated receptor (PPAR) agonists FDA-approved in adults for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA or ursodiol) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA.
- II. Primary biliary cholangitis (PBC) is a rare, autoimmune, cholestatic liver disease that impacts nearly 100,000 people in the United States (U.S.). Most patients diagnosed with PBC are 40 to 60 years old. Primary biliary cholangitis (PBC) is characterized by a T-lymphocyte-mediated attack on small intralobular bile ducts and bile ducts are destroyed and as a result leading to a build-up of bile, toxins, and chronic inflammation, which causes irreversible fibrosis of the liver. Given the complexity of diagnosis and management of PBC, the treatment must be initiated by, in or consultation with a gastroenterologist or hepatologist.
- III. Primary biliary cholangitis (PBC) is considered when patients have an elevated alkaline phosphatase (ALP) without extrahepatic biliary obstruction and symptoms of unexplained itching, fatigue, or jaundice. A diagnosis of PBC is made when there is no evident extrahepatic biliary obstruction, no comorbidity affecting the liver, and at least two of the following are

present: an alkaline phosphatase at least 1.5 times the upper limit of normal (44-147 IU/L), presence of antimitochondrial antibodies (AMA) at a titer of 1:40 or higher (or other PBC specific autoantibodies), or histologic evidence of PBC. The 2018 American Association for the Study of Liver Diseases (AASLD) guidelines recommend ursodeoxycholic acid (UDCA or ursodiol) as first line therapy for treatment of PBC. Unfortunately, 30-40% of patients do not respond to UDCA and will require the addition of obeticholic acid (Ocaliva). Guidelines recommend treatment with UDCA for at least 12 months prior to treatment escalation. Despite the 12-month recommendation, guidelines acknowledge that 90% of the improvement on UDCA usually occurs within 6 to 9 months. Numerous studies support that the effect of UDCA generally plateaus after 6 months.

- An observational study published in April 2023 found that a 6-month biochemical response pattern is a good predictor of insufficient response to UDCA. At 6 months, there were 235 patients with ALP $>1.9 \times$ ULN which did not meet biochemical response. Of these patients, 89% did not achieve biochemical response after one year of UDCA. Collectively, there is moderate confidence that lack of response to UDCA after 6 months warrants treatment escalation.
- IV. Obeticholic acid (Ocaliva) was studied in a randomized, double-blind, placebo-controlled Phase 3 trial (POISE). The study included 216 adults aged 18 years and older with a diagnosis of PBC (defined by presence of two of the following: alkaline phosphatase (ALP) elevated for ≥ 6 months prior to randomization, positive anti-mitochondria titer, or liver biopsy consistent with PBC). Participants were randomized to receive obeticholic acid (Ocaliva) 5mg, 10mg, or placebo daily, in combination with UDCA. Participants in the lower dose cohort were started on 5mg daily for six months, then given the option to increase to 10mg daily for the last six months. Baseline characteristics were similar between both cohorts, with a mean age of 56 years, mostly female (94%) and most participants were receiving concurrent UDCA (93%). Obeticholic acid (Ocaliva) 10mg and 5mg titration cohorts showed a statistically significantly higher proportion of participants achieving biochemical response compared to placebo over 52 weeks, 48% vs 10%, difference 38%, $p < 0.0001$ and 46% vs 10%, difference 46%, $p < 0.0001$, respectively. Biochemical response defined as ALP level < 1.67 times the upper limit of the normal range [ULN], with a decrease of $\geq 15\%$ from baseline, and a normal total bilirubin level.
- The rate of adverse events occurred more frequently in the obeticholic acid (Ocaliva) 10mg, titration group compared to placebo. The most reported adverse events were pruritis (70%, 56%, 38%), fatigue (25%, 19%, 15%), rash (10%, 7%, 8%), and arthralgia (10%, 6%, 4%). Obeticholic acid (Ocaliva) has black box warnings for hepatic decompensation and failure and is contraindicated in decompensated cirrhosis. Significant post marketing liver failure, new onset cirrhosis, increased direct and total bilirubin or worsening of jaundice was reported. Due to risk of serious liver injury, the FDA restricted use of obeticholic acid (Ocaliva) in patients with PBC and advanced cirrhosis. Obeticholic acid (Ocaliva) is not to be used in patients with cirrhosis with evidence of portal hypertension (which signifies progression to decompensated cirrhosis).
- V. Elafibranor (Iqirvo) was studied in a randomized, placebo-controlled, double-blind, Phase 3 study. The study included 161 adults aged 18 to 75 years with a diagnosis of PBC (defined by presence of two of the following: ALP elevated for ≥ 6 months prior to randomization, positive anti-mitochondria titer, or liver biopsy consistent with PBC). Participants were randomized to receive elafibranor (Iqirvo) 80 mg or placebo daily with UDCA. Baseline characteristics were similar between both cohorts, with a mean age of 57 years, mostly female (96%) and most participants were receiving concurrent UDCA (95%). Elafibranor group had a statistically

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significantly higher proportion of participants achieving biochemical response compared to placebo over 52 weeks (51% vs. 4%), difference of 47% (95% CI: 32, 57; $p < 0.001$). Biochemical response defined as ALP level < 1.67 times the upper limit of the normal range [ULN], with a decrease of $\geq 15\%$ from baseline, and a normal total bilirubin level. Elafibranor (Iqirvo) did not demonstrate a statistically significant difference in the pruritic NRS score compared to placebo, -0.78 ($p = 0.20$).

- The rate of adverse events was similar between elafibranor (Iqirvo) and placebo. Gastrointestinal symptoms (abdominal pain, diarrhea, vomiting, and nausea) occurred more often in the elafibranor (Iqirvo) group compared to placebo (11% vs 2-9%). Pruritus (20.4% vs 26.4%) and fatigue (9.3% vs 13.2%) occurred less often in the elafibranor (Iqirvo) group. Four participants discontinued treatment with elafibranor (Iqirvo) due to increased creatine phosphokinase levels. Deaths occurred in two patients (1.9%) in the elafibranor (Iqirvo) group: one postoperative complication after abdominal hernia repair and one participant died from biliary sepsis and acute kidney injury. Both deaths were not deemed to be treatment related.
- There are no specific contraindications to using elafibranor (Iqirvo). Warning and precautions for elafibranor (Iqirvo) include myalgia, myopathy, and rhabdomyolysis, fractures, adverse effects on fetal and newborn development, drug-induced liver injury, hypersensitivity reactions, and biliary obstruction.

VI. Seladelpar (Livdelzi) was studied in a randomized, placebo-controlled, double-blind, Phase 3 study. The study included 193 adults aged 18 to 75 years with a diagnosis of PBC (defined by presence of two of the following: alkaline phosphatase (ALP) elevated for ≥ 6 months prior to randomization, positive anti-mitochondria titer, or liver biopsy consistent with PBC). Participants were randomized to receive seladelpar (Livdelzi) 10 mg or placebo daily with UDCA. Baseline characteristics were similar between both cohorts, with a mean age of 57 years, mostly female (95%) and most participants were receiving concurrent UDCA (93%). A greater percentage of the patients in the seladelpar (Livdelzi) group than in the placebo group had a biochemical response (61.7% vs. 20.0%; difference, 41.7 percentage points; 95% confidence interval [CI], 27.7 to 53.4, $P < 0.001$). Biochemical response defined as ALP level < 1.67 times the ULN, with a decrease of $\geq 15\%$ from baseline, and a normal total bilirubin level. Seladelpar (Livdelzi) demonstrated a statistically significant decrease from baseline in pruritic NRS score compared to placebo, -1.5 ($p = 0.005$). However, a change of -1.5 in pruritic NRS is not considered clinically significant.

- The rate of adverse events was similar between seladelpar (Livdelzi) and placebo. Adverse events that occurred more often in the seladelpar (Livdelzi) group included headache (7.8% vs. 3.1%), abdominal pain (7.0% vs. 1.5%), nausea (6.2% vs. 4.6%), and abdominal distention (6.2% vs. 3.1%). Pruritis occurred less often in the seladelpar (Livdelzi) group (4.7% vs 15.4%). Four participants discontinued treatment with seladelpar (Livdelzi) due to disease progression, increased liver function test, coagulopathy, and papillary thyroid cancer.
- There are no specific contraindications to using seladelpar (Livdelzi). Warning and precautions for seladelpar (Livdelzi) include fractures, liver test abnormalities, and biliary obstruction.

VII. Elafibranor (Iqirvo) and seladelpar (Livdelzi) are not recommended in patients with decompensated cirrhosis (e.g. ascites, variceal bleeding, and hepatic encephalopathy). The safety and efficacy of both drugs in patients with decompensated liver disease has not been established. Patients should be monitored for evidence of decompensation and product(s) may be considered for discontinuation if patients progress to moderate or severe hepatic impairment.

- VIII. Biochemical response is a validated outcome commonly used in PBC trials. Levels of ALP and bilirubin have been shown predict clinical outcomes (e.g. delayed liver transplantation or death) in patients with PBC. Studies have demonstrated that an improved/normalized ALP and bilirubin are directly related to liver-transplant free survival. In patients with ALP <1.67 x ULN and bilirubin normalization (total bilirubin less than 1mg/dL), the 10-year transplant free survival rate is 86% compared to 34% in patients with an uncontrolled ALP and bilirubin.
- IX. Obeticholic acid (Ocaliva), elafibranor (Iqirvo) and seladelpar (Livdelzi) were FDA-approved under the accelerated approval pathway based on biochemical response on reduction in alkaline phosphatase (ALP) and continued approval for the treatment of PBC is contingent upon verification and description of clinical benefit in confirmatory trials. Prevention of liver decompensation events and clinically meaningful reduction in pruritis have not been established at this time.

Investigational or Not Medically Necessary Uses

- I. Obeticholic acid (Ocaliva), elafibranor (Iqirvo), and seladelpar (Livdelzi) have not been sufficiently evaluated in the following settings:
 - A. Metabolic Dysfunction-Associated Steatohepatitis (MASH)/Non-alcoholic steatohepatitis (NASH)
 - i. Obeticholic acid (Ocaliva) for treatment of MASH was rejected by the FDA in 2020 due to an inability to demonstrate clinical benefit.
 - ii. Elafibranor was studied in an international, randomized, double-blinded, placebo-controlled trial (RESOLVE-IT) to evaluate resolution of NASH. Participants were randomized to receive elafibranor 80 mg, 120 mg, or placebo daily for 52 weeks. The study did not find a significant difference between the elafibranor and placebo groups. Additionally, no significant differences as compared to placebo were achieved in the key secondary endpoints, including fibrosis improvement of at least one stage and changes in metabolic parameters (PMID: 26874076).
 - iii. According to the practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association, first line treatment for NASH is weight loss as it generally reduces hepatic steatosis, achieved either by hypocaloric diet alone or in conjunction with increased physical activity. Loss of at least 3-5% of body weight appears necessary to improve steatosis, but a greater weight loss (up to 10%) may be needed to improve necroinflammation.
 - B. Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)/Non-alcoholic fatty liver disease (NAFLD)
 - C. Familial partial lipodystrophy
 - D. Obesity
 - E. Digestive system disease/symptoms (bile acid diarrhea, unspecified diarrhea, gallstones, primary sclerosing cholangitis, biliary atresia, etc.)

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Related Policies

Currently there are no related policies.

Policy Implementation/Update

Action and Summary of Changes	Date
Elafibranor (Iqirvo) and seladelpar (Livdelzi) added to policy based on new FDA approval. Supporting evidence of obeticholic acid (Ocaliva) updated. References updated.	11/2024
Removed generic obeticholic acid from policy until available on the market	02/2024
Added E/I supporting evidence for NASH indication and digestive system disease/symptoms. Updated supporting evidence for PBC. Updated references. Added related policies.	06/2023
Added generic obeticholic acid to policy QL table, require use of generic prior to brand	05/2023
Added supporting evidence for the investigational use in NASH	07/2020
Prior authorization criteria transitioned to policy format. Updated initial and renewal durations. Addition of specialist requirements. Addition of confirmed diagnosis and Child Pugh A classification. Further clarification of characteristics of inadequate response to ursodeoxycholic acid. Addition of renewal criteria.	12/2019
Policy created	06/2016

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP001

Description

Alirocumab (Praluent) and evolocumab (Repatha) are subcutaneous Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) inhibitors.

Length of Authorization

- Length of Benefit

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
alirocumab (Praluent)	Heterozygous familial hypercholesterolemia; Homozygous familial hypercholesterolemia;	75 mg/mL pen injector	2 mL (2 pens)/28 days
		150 mg/mL pen injector	
evolocumab (Repatha)	Atherosclerotic cardiovascular disease; Non-familial hypercholesterolemia	140 mg/mL auto injector pen; prefilled syringe	2 mL (2 pens; PFS)/28 days
		420 mg/mL solution cartridge	3.5 mL (1 cartridge)/28 days

Initial Evaluation

- I. **Alirocumab (Praluent) or evolocumab (Repatha)** may be considered medically necessary when the following criteria below are met:
 - A. The member has an LDL-C level greater than, or equal to, 70 mg/dL while on maximally tolerated statin therapy; **AND**
 - B. If the request is for alirocumab (Praluent), treatment with evolocumab (Repatha) has been ineffective, not tolerated, or contraindicated; **AND**
 - C. Therapy with a high intensity statin (greater than, or equal to, atorvastatin [Lipitor] 40 mg or rosuvastatin [Crestor] 20 mg) for at least an 8-week duration has been ineffective; **AND**
 1. The member will continue statin therapy in combination with alirocumab (Praluent) or evolocumab (Repatha); **OR**
 - D. Provider attestation that there is clinical documentation of statin failure defined by one of the following:
 1. Treatment with maximally tolerated doses of any statin (e.g., simvastatin [Zocor], pravastatin [Pravachol], etc.) was ineffective or contraindicated; **OR**
 2. The member has not tolerated at least two statin medications as defined by at least one of the following:
 - i. CK exceeds 10 times the upper limit of normal
 - ii. LFTs exceed 3 times the upper limit of normal
 - iii. Severe muscle weakness inhibiting activities of daily living, employment, or leading to temporary disability; **OR**

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3. The member experienced severe rhabdomyolysis after the use of at least one statin; **AND**
- E. A diagnosis of one of the following:
1. **Atherosclerotic cardiovascular disease (ASCVD); AND**
 - i. Member is 18 years of age or older; **AND**
 - ii. Attestation that there is clinical documentation supporting a diagnosis clinical atherosclerotic disease via invasive or non- invasive testing (e.g., stress test, imaging); **OR**
 - iii. Diagnosis of atherosclerotic disease and primary prevention failure (e.g., member has had a stroke, myocardial infarction); **OR**
 2. **Heterozygous familial hypercholesterolemia; AND**
 - i. The member is 10 years of age or older; **OR**
 - a. The member is 8 years of age or older and the request is for alirocumab (Praluent); **AND**
 - ii. Diagnosis of heterozygous familial hypercholesterolemia is confirmed by one of the following
 - a. Genotyping or clinical criteria using either the Simon Broome diagnostic criteria (definite diagnosis classification) or Dutch Lipid Network criteria (score greater than 8)
 - b. Attestation that there is clinical documentation or a DNA mutation analysis supporting the diagnosis of heterozygous familial hypercholesterolemia; **OR**
 3. **Homozygous familial hypercholesterolemia; AND**
 - i. The member is 18 years of age or older; **OR**
 - a. The member is 10 years of age or older and the request is for evolocumab (Repatha); **AND**
 - ii. The member has a history of an untreated LDL-cholesterol level greater than 500 mg/dL with either evidence of heterozygous familial hypercholesterolemia in both parents or xanthoma before the age of 10; **OR**
 - a. Attestation that there is documentation of DNA mutation analysis supporting the diagnosis of homozygous familial hypercholesterolemia (e.g, *LDLR*, *APOB*, *PSCK9*, *LDLRAP1*); **AND**
 - iii. Evolocumab (Repatha) or alirocumab (Praluent) will not be used in combination with lopitamide (Juxtapid)
 4. **Non-familial hypercholesterolemia; AND**
 - i. The member is 18 years of age or older; **AND**
 - ii. The member has a history of an untreated LDL-C level greater than, or equal to, 190 mg/dL; **AND**
 - iii. Treatment with ezetimibe (Zetia) has been ineffective, contraindicated, or not tolerated; **AND**
 - iv. The member is unable to achieve ≥50% LDL-C reduction and LDL-C <100 mg/dL or non-HDL-C <130 mg/dL on maximally tolerated cholesterol lowering therapy; **AND**

- v. Provider attestation hypercholesterolemia is not due to a reversible/untreated secondary cause (e.g. hypothyroidism, nephrotic syndrome, primary biliary cholangitis)
- II. Alirocumab (Praluent) or evolocumab (Repatha) are considered investigational when used for all other conditions, including but not limited to:
 - A. ASCVD primary prevention in non-familial hypercholesterolemia with untreated LDL-C < 190 mg/dL

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Member has experienced a decrease from baseline LDL-C while on therapy; **AND**
- IV. If the request is for alirocumab (Praluent), treatment with evolocumab (Repatha) has been ineffective, not tolerated, or contraindicated

Supporting Evidence

- I. Alirocumab (Praluent) is FDA-approved to reduce the risk of myocardial infarction, stroke, and unstable angina requiring hospitalization in adults with established cardiovascular disease and as an adjunct to diet, alone, or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for the treatment of patients 10 years and older with primary hyperlipidemia (including heterozygous familial hypercholesterolemia) or homozygous familial hypercholesterolemia who require additional lowering of low-density lipoprotein cholesterol (LDL-C).
- II. Evolocumab (Repatha) is FDA-approved to reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established cardiovascular disease and as an adjunct to diet, alone or in combination with other lipid-lowering therapies (e.g., statins, ezetimibe), for treatment of patients 10 years and older with primary hyperlipidemia (including heterozygous familial hypercholesterolemia) or homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.
- III. The 2017 American Association of Clinical Endocrinologists (AACE) guidelines state statin therapy is recommended as the primary pharmacologic agent to achieve target LDL-C goals on the basis of morbidity and mortality outcome trials. Additionally, guidelines state PCSK9 inhibitors should be considered in individuals with clinical cardiovascular disease who are unable to reach LDL-C/non-HDL-C goals with maximally tolerated statin therapy. They should not be used as monotherapy except in statin-intolerant individuals.
- IV. Seventy to ninety percent of patients are able to tolerate an alternate long-term statin. In clinical practice, 10-25% of patients have musculoskeletal adverse events associated with statin use; however, several studies have determined that the majority of patients with statin-

associated muscle symptoms are able to tolerate subsequent statin therapy with modified dosing regimens.

- V. The 2011 National Lipid Association (NLA) familial hypercholesterolemia guidelines define ineffective therapy as inability to achieve an LDL-C of less than 70 mg/dL with treatment in atherosclerotic cardiovascular disease.
- VI. **Atherosclerotic cardiovascular disease (ASCVD):** 2018 American Heart Association/American College of Cardiology (AHA/ACC) Cholesterol Guidelines recommend patients with clinical ASCVD reduce LDL-C with high-intensity statin therapy or maximally tolerated statin therapy. In patients with clinical ASCVD who are judged to be very high risk and considered for PCSK9 inhibitor therapy, maximally tolerated LDL-C lowering therapy should include maximally tolerated statin therapy and ezetimibe (very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions).
- The 2017 American College of Cardiology (ACC) Recommendations for Non-Statins Therapy recommends consideration of adding ezetimibe first in patients that are statin intolerant with clinical ASCVD and may consider a bile acid sequestrant as an alternative if ezetimibe intolerant and triglycerides <300 mg/dL.
 - Ezetimibe is a clinically appropriate and cost-effective alternative to PCSK9 inhibitors in scenarios where addition of ezetimibe would be expected to bring LDL-C levels to a patient specific LDL-C goal. In patients with ASCVD, the 2018 AHA/ACC Cholesterol Guidelines recommend achieving a $\geq 50\%$ reduction in LDL-C levels and an LDL-C goal of <70mg/dL. The 2021 European Society of Cardiology Guidelines recommend lipid-lowering treatment with an ultimate goal of <55mg/dL and a $\geq 50\%$ reduction of LDL-C from baseline. Depending on specific risk factors, providers may choose different LDL-C goals for their patients. Ezetimibe is cited to lower LDL-C by 15-20% when used by itself or in combination with a statin. Therefore, information about patient's specific LDL-C goals and concomitant cholesterol lowering therapies is required to estimate overall LDL-C lowering effect and assess appropriateness of treatment with ezetimibe.
 - Per Schmidt et al. Cochrane Review, "In comparisons of PCSK9 inhibitors versus no PCSK9 inhibitors, current evidence suggests that PCSK9 inhibitors decrease CVD incidence without affecting the incidence of all-cause mortality. In comparisons of PCSK9 inhibitors versus alternative (more established) treatments such as statins or ezetimibe, high-quality evidence is lacking. Differences in risk between people treated with and without PCSK9 inhibitors suggest the absolute treatment benefit will likely be modest (e.g., < 1% change in risk)."
- VII. Insight from cardiology specialists indicate that diagnosis of clinical ASCVD in the absence of a cardiovascular event can be achieved by angiography, ischemia on stress test, or stenosis of 50% or more using other imaging techniques. While evidence of coronary calcification on CTA (calcium score >1) is indicative of high-risk of developing ASCVD, this number should be integrated into the member's clinical profile to determine individual patient risk and treatment but should not necessarily be used alone for the purposes of clinical diagnosis.
- VIII. **Heterozygous familial hypercholesterolemia:** The presence of tendon xanthoma is a genetically modulated clinical syndrome of familial hypercholesterolemia. In addition, DNA testing can be used to diagnose familial hypercholesterolemia functional mutations. In clinical trials, enrolled

patients with heterozygous familial hypercholesterolemia were diagnosed either by genotyping or clinical criteria ("definite FH" using either the Simon Broome or Dutch Lipid Network).

Simon Broome Familial Hypercholesterolemia Register diagnostic criteria for familial hypercholesterolemia	
Criteria	Description
A	Total cholesterol concentration above 7.5 mmol/liter (290 mg/dL) in adults or a total cholesterol concentration above 6.7 mmol/liter (259 mg/dL) in children aged less than 16 years, or
	Low density lipoprotein cholesterol concentration above 4.9 mmol/liter (189 mg/dL) in adults or above 4.0 mmol/liter (155 mg/dL) in children
B	Tendinous xanthomata in the patient or a first-degree relative
C	DNA-based evidence of mutation in the <i>LDLR</i> , <i>PCSK9</i> , or <i>APOB</i> gene
D	Family history of myocardial infarction before age 50 years in a second-degree relative or before age 60 years in a first-degree relative
E	Family history of myocardial infarction before age 50 years in a second-degree relative or before age 60 years in a first-degree relative
A "definite" FH diagnosis requires either criteria a and b, or criterion c. A "probable" FH diagnosis requires either criteria a and d, or criteria a and e.	
Dutch Lipid Clinic Network diagnostic criteria for familial hypercholesterolaemia	
Criteria	Points
Family history	
- First-degree relative with known premature (men: <55 years; women: <60 years) coronary or vascular disease, or - First-degree relative with known LDL-C above the 95th percentile	1
- First-degree relative with tendinous xanthomata and/or arcus cornealis, or - Children <18 years of age with LDL-C above the 95th percentile	2
Clinical History	
Patient with premature (men: <55 years; women: <60 years) coronary artery disease	2
Patient with premature (men: <55 years; women: <60 years) cerebral or peripheral vascular disease	1
Physical examination	
Tendinous xanthomata	6
Arcus cornealis before age 45 years	4
LDL-C levels	
LDL-C ≥ 8.5 mmol/L (325 mg/dL)	8
LDL-C 6.5-8.4 mmol/L (251-325 mg/dL)	5
LDL-C 5.0-6.4 mmol/L (190-250 mg/dL)	3
LDL-C 4.0-4.9 mmol/L (155-189 mg/dL)	1
DNA analysis	
Functional mutation in the <i>LDLR</i>, <i>apoB</i>, or <i>PCSK9</i> gene	8
Choose only one score per group, the highest applicable diagnosis	

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(diagnosis is based on the total number of points obtained)

- A "definite" FH diagnosis requires >8 points
- A "probable" FH diagnosis requires 6-8 points
- A "possible" FH diagnosis requires 3-5 points

- Using DNA testing, patients with familial hypercholesterolemia (FH) have been identified as generally having a functional mutation of one of three genes: *LDLR*, *PCSK9*, or *APOB* gene. Mutations in these three genes can be detected in about 80 percent of patients with the definite FH clinical syndrome.
- The 2017 AACE guidelines state PCSK9 inhibitors should be considered for use in combination with statin therapy for LDL-C lowering in individuals with FH.

IX. **Homozygous familial hypercholesterolemia (HoFH):** Evolocumab (Repatha) and alirocumab (Praluent) are FDA-approved in the setting of HoFH and includes patients ages 13 and older (Repatha) or 18 and older (Praluent). Evolocumab (Repatha) was studied in one multi-center, double-blind, randomized, placebo-controlled trial (TESLA Part B) in patients greater than, or equal to, 13 years of age with homozygous familial hypercholesterolemia. Patients in the clinical trial had familial hypercholesterolemia diagnosed either by genetic analysis or clinical criteria (history of an untreated LDL cholesterol concentration >13 mmol/L (500 mg/dL)) plus either xanthoma before 10 years of age or evidence of heterozygous familial hypercholesterolemia in both parents. Alirocumab (Praluent) was studied in one randomized, double-blind, placebo-controlled, parallel-group, phase 3 study (ODYSSEY HoFH) in patients 18 years of age or older with homozygous familial hypercholesterolemia. Patients in the clinical trial had a diagnosis of familial hypercholesterolemia confirmed in the patient's medical history by clinical diagnosis or by genotyping. The genotyping results from this study found patients had mutations in the *LDLR*, *LDLRAP1*, *PCSKP*, or *APOB* genes.

- Use of evolocumab (Repatha) and alirocumab (Praluent) with mipomersen (Kynamro) or lopitamide (Juxtapid) has not been studied in a large population, and the efficacy and safety is unknown. Concurrent use is considered experimental and investigational.

X. **Non-familial hypercholesterolemia**

- The use of statins, including in patients considered to be high risk, is recommended as first line therapy by multiple guidelines. Statins have pleiotropic effects, which involves improvement of endothelial function, decreasing oxidative stress and inflammation, enhancing stability of atherosclerotic plaques, and inhibiting thrombogenic response. These pleiotropic effects have been hypothesized for PCSK9 inhibitors in preclinical studies but have not yet been established.
- Long term risk of ASCVD or CHD (defined as CHD death or non-fatal MI) in adults with familial hypercholesterolemia phenotype (defined as LDL-C levels $\geq$ 190 mg/dL, irrespective of genetic confirmation of true familial hyperlipidemia or family history of cardiovascular disease) was evaluated using pooled data from 6 large epidemiological studies consisting of 68,565 patients between 20 and 79 years old. The reference group were patients with LDL-C <130 mg/dL. Sensitivity analyses were utilized for patients with LDL-C levels $\geq$ 190 mg/dL and positive family history. Statin or other hyperlipidemia medications were not specifically reported out within the trial, but it was noted that the vast majority of the data were collected before

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widespread use of statins. Rate of cholesterol treatment at baseline were very low, between 0% and 4.4% for the different analysis arms, with slightly higher but statistically significant usage within the ≥ 190 mg/dL population for certain age groups. Baseline characteristics were largely the same, but there were statistically significant higher proportion of smokers and hypertension treatment at baseline in the LDL ≥ 190 mg/dL. Overall, adjusted for age, race, BMI, DM, smoking, blood pressure treatment, patients with LDL ≥ 190 mg/dL were at 1.3 (95% CI 1.0-1.7) to 5.0 (95% CI 1.1-21.7) times higher risk of CHD and up to 4.1x higher total risk of ASCVD (HR 4.1 (95% CI, 1.2-13.4). Hazard ratios for CHD risk decreased with age but was significant in all age groups except those between 70-79 years old (HR 1.3; 95% CI 1.3 (1.0-1.7)). This study demonstrated that irrespective of genetic confirmation of familial hyperlipidemia or family history of cardiovascular disease, patients with LDL-C levels ≥ 190 mg/dL, were at 2-5x higher risk of CHD, and up to 4x higher risk for ASCVD.

- Khera et al. assessed the relationship between severe hypercholesterolemia (defined as untreated LDL-C ≥ 190 mg/dl) and CAD risks, found that among 20,485 CAD-free and prospective cohort participants, 1,386 (6.7%) had LDL ≥ 190 mg/dL, and of those, gene sequencing only identified 24 patients (1.7%) with FH mutation. Compared to reference group of LDL <130 mg/dl and no mutation, those with LDL ≥ 190 mg/dL and had no FH mutation were at 6x higher risk for CAD (OR 6.0; 95% CI 5.2-6.9), and those with ≥ 190 mg/dL and FH mutation were at 22x higher risk (OR 22.3; 95% CI (10.7-53.2)). This data suggests that even patients without confirmed genetic familial hypercholesterolemia but severe untreated LDL-C ≥ 190 mg/dL are at significantly higher risk of developing CAD.
- A systematic review and meta-analysis containing a total of 312,175 patients from 49 trials among different therapeutic interventions demonstrated a relative risk for major vascular events per 1-mmol/L (38.7 mg/dL) reduction in LDL-c level was 0.77 (95% CI, 0.71-0.84; $p < 0.001$) for statins and 0.75 (95% CI, 0.66-0.86; $P = 0.002$) for non-statin therapies. The meta-analysis consisted of trials assessing statins (25), ezetimibe (1), fibrates (9), niacin (3), CETP inhibitors (3), diet (4), bile acid sequestrants (2), ileal bypass (1), and PCSK9-inhibitors (2). Primary prevention trials achieved 1.5% (95% CI, 0.5%-2.6%) lower event rate of major coronary events per each 38.7 mg/dL LDL-C level reduction ($p = 0.008$) and secondary prevention trials achieved 4.6% (95% CI, 2.9%-6.4%) lower event rate per 38.7 mg/dL LDL-C level reduction ($p < 0.001$). Major vascular events included: cardiovascular death, acute MI or other ACS, coronary revascularization, or stroke. The two PCSK9 inhibitor studies (ODYSSEY Long Term and OSLER) consisted of 6,808 patients and demonstrated a 0.49 relative risk (95% CI, 0.34-0.71) between treatment and control groups for each 38.7 mg/dL reduction in LDL. ODYSSEY and OSLER contained both primary and secondary prevention patients in conjunction with evidence that PCSK-9 inhibitors
- OSLER-1 and OSLER-2 were longer-term Open-Label extension trials for five Phase 2 (MENDEL-1, LAPLACE-TIMI 57, GAUSS-1, RUTHERFORD-1, YUKAWA-1) and seven Phase 3 trials (MENDEL-2, LAPLACE-2, GAUSS-2, RUTHERFORD-2, DECSCARTES, THOMAS-1, THOMAS-2) evaluating evolocumab. OSLER demonstrated a 1.23%

absolute risk reduction of cardiovascular events (i.e. death, MI, unstable angina requiring hospitalization, coronary revascularization, stroke, transient ischemic attack, heart failure hospitalization) between evolocumab plus standard of care group vs standard of care alone group at 1 year (0.95% vs 2.18%, respectively). With regards to LDL-C lowering, evolocumab demonstrated greater than 70 mg/dL absolute reduction in LDL-C by 12 weeks, and approximately a 60% reduction in LDL-C. This reduction in LDL-C was sustained at every time point through 48 weeks. About 10% of patients enrolled in OSLER had known familial hypercholesterolemia, 20% had coronary artery disease, 24% had family history of premature coronary artery disease, and 9% had cerebrovascular or peripheral artery disease. The patient characteristics of these trials demonstrate that statistically significant absolute risk reduction of cardiovascular events can be achieved even when the majority of patients did not have familial hypercholesterolemia or coronary artery disease at baseline.

- The DESCARTES trial, a 52-week randomized placebo-controlled trial containing 901 adult patients between 18 and 75 years old with LDL cholesterol of ≥ 75 mg/dL and fasting triglyceride of ≤ 400 mg/dL. After a 4-week run-in period, patients with CHD or CHD risk equivalent and LDL < 100 mg/dL, or no CHD or CHD risk equivalent and LDL < 130 mg/dL, or on maximal background therapy were randomized 2:1 to evolocumab 420mg SC Q4W or Placebo between 4 different treatment arms; patients treated with diet alone, patients treated with diet and atorvastatin 10 mg, patients treated with diet and atorvastatin 80mg, and patients treated with diet, atorvastatin 80mg and ezetimibe 10mg. At baseline, 15.1% of patients had coronary artery disease, but prevalence of familial hyperlipidemia was not reported. Given the mean baseline LDL-C was between 94.6 to 119.8 mg/dL, the proportion of patients with familial hyperlipidemia is expected to be relatively low compared to the overall study population. Overall, the DESCARTES study demonstrated a statistically significant $-57.0\% \pm 2.1\%$ mean change from baseline in LDL between evolocumab and placebo group at 52 weeks. Eighty-two point 3 percent of patients achieved LDL of < 70 mg/dL at 52 weeks, compared to 6.5% for the placebo group. Roughly 1/3rd of the patients that achieved LDL < 70 mg/dL while on placebo at 52 weeks were from the diet plus 80mg atorvastatin plus ezetimibe 10mg arm. Within this treatment arm, there was a -48.5 ± 5.2 mean difference in percent change from baseline LDL cholesterol at 52 weeks of treatment. The DESCARTES trial demonstrated that even while on max dose high intensity statin and ezetimibe, the addition of a PCSK9-inhibitor can still achieve significant reduction in LDL cholesterol levels from baseline.
- Per 2022 ACC Expert Consensus Decision Pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk, there is a pathway for consideration of PCSK9 inhibitors for adults without clinical ASCVD and with baseline LDL-C ≥ 190 mg/dL not due to secondary causes who are taking statin therapy for primary prevention. The panel recommends the addition of ezetimibe and/or PCSK9 inhibitors to maximally

tolerated statin therapy if LDL-C reduction of $\geq 50\%$ LDL-C reduction and LDL-C < 100 mg/dL or non-HDL-C < 130 mg/dL is not achieved.

- Secondary causes of hypercholesterolemia are caused by medications, substances, and medical conditions leading to elevated levels of LDL and other lipids. Hypothyroidism, nephrotic syndrome, primary biliary cholangitis, and diabetes have the most supporting evidence to suggest a link between the condition and secondary elevation of lipid levels, specifically LDL cholesterol. In line with the recommendations from the 2018 ACC/AHA guidelines and 2022 ACC Expert Consensus recommendations, LDL elevation due to secondary causes does not warrant the same level of consideration for treatment with the exception of diabetes. Although diabetes is an established secondary cause of hypercholesterolemia, the condition is also a significant risk factor that warrants additional and more intensive lipid lowering to reduce the risk of atherosclerosis.
- Safety and efficacy of PCSK9 inhibitors, specifically Repatha (evolocumab) has not been established in non-familial hyperlipidemia pediatric patients.

Investigational or Not Medically Necessary Uses

- I. ASCVD Primary prevention non-familial hypercholesterolemia with LDL-C < 190 mg/dL
 - A. Currently, there is no established data to support the use of PCSK-9 inhibitors in the primary prevention setting for patients with an LDL-C level below 190 mg/dL. In accordance with the 2022 ACC Expert Consensus statement and 2023 American Diabetes Association Standards of Care in Diabetes Guidelines, in the absence of ASCVD or baseline LDL-C 190 mg/dL, PCSK-9 inhibitors do not have an established, evidence-based role for primary prevention of ASCVD. For patients without ASCVD and have an LDL-C of 70-189 mg/dL, the ACC Expert writing committee does not routinely recommend PCSK9 inhibitors given limited efficacy data and low cost-effectiveness in primary prevention patients on statin therapy.
 - B. According to the 2018 AHA/ACC clinical guidelines, patients with an LDL-C of ≥ 190 mg/dL in primary prevention or secondary prevention are at a higher risk of future ASCVD events, and do not require a risk assessment before starting lipid lowering therapy. Patients with a baseline LDL-C between 70 mg/dL and 189 mg/dL are at lower risk of future ASCVD events, and ASCVD risk assessment is warranted before initiation of therapy. The use of statin is recommended as the first line treatment option for these patients.
 - C. Within the 2022 ACC Expert Consensus statement, an LDL-C cutoff of 190 mg/dL is utilized for direct management to PCSK9 inhibitors. For adults with possible statin intolerance without clinical ASCVD and LDL-C < 190 mg/dL, ezetimibe is considered the first line non-statin therapy, and bile acid sequestrants are considered second-line therapy. PCSK9 inhibitors are not included in this recommendation pathway unless a member has clinical ASCVD or an LDL-C > 190 mg/dL. Standard LDL-C scales and lipid panels consider an LDL of 160-189 mg/dL as high, and LDL of ≥ 190 mg/dL as very high or severely elevated. An LDL of 160-189 mg/dL in primary hypercholesterolemia is considered a risk-enhancing factor for clinician-patient risk discussion.
- A 14,570-participant cohort study presented at the American Heart Association 2021 Scientific Sessions compared the risk of major adverse cardiovascular events (MACE) in

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the next 10 years in patients between 20-39 years old with an LDL-C of 160-189 mg/dL to patients with an LDL-C of less than 160 mg/dL. Results showed that the risk of MACE were not significantly different between the two groups (OR. 1.28 [95% CI, 0.94-1.74; p <0.115). MACE was defined as all-cause death, MI, ischemic stroke, heart failure hospitalization, and peripheral vascular disease. While there was not a comparison cohort of patients with LDL-C > 190mg/dL in this study, the result is in line with the understanding that patients with an LDL-C of <190 mg/dL are not at a significantly higher risk for ASCVD and major adverse cardiovascular events, even if their LDL-C is elevated at 160-189 mg/dL.

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Policy Implementation/Update:

Action and Summary of Changes	Date
Updated approval length to length of benefit	08/2025
Updated to include Praluent age expansion in pediatric patients aged 8 years and older with heterozygous familial hypercholesterolemia (HeFH). Removed specialist prescribing requirement.	07/2024
Addition of non-familial hypercholesterolemia criteria and supporting evidence. Removed not medically necessary criteria for Hypercholesterolemia non-familial cause indication, and added ASCVD primary prevention non-familial hypercholesterolemia with LDL-C 190mg/dl to experimental and investigational criteria. Minor formatting changes.	02/2023
Updated to allow provider attestation in HoFH DNA mutation analysis. Require history with only one statin in the setting of previous rhabdomyolysis.	01/2023
Removed ezetimibe step criteria for ASCVD. Included trial of Repatha prior to Praluent within initial and renewal criteria.	12/2022
Added criteria allowing a path to coverage in scenarios where ezetimibe would not be expected to bring LDL-C levels to a desired LDL-C goal. Updated supporting evidence.	08/2022
Updated to include age expansion in pediatric patients aged 10 years and older with heterozygous familial hypercholesterolemia (HeFH) or homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C	02/2022
Added new FDA-approved indication of HoFH for Praluent. Updated diagnosis confirmation requirements for HeFH and HoFH to align with current guidelines. Removed statement around combination use with Kynamro as product has been discontinued. Update to supporting evidence.	04/2021
Review. Update to supporting evidence	12/2020
Updated to policy format. Added requirement of ezetimibe trial and failure in ASCVD.	06/2019
Addition of Repatha 420mg/3.5mL pushtronex system to the approval language.	11/2018
Removed alternate statin dosing strategies in patients who are statin intolerant. Decreased LDL cutoff to >70 for all indications. Increased initial authorization to 12 months. Removed requirement to try and fail statin plus Zetia combination therapy. Removed DNA mutation analysis confirming homozygous familial	06/2018

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hypercholesterolemia diagnosis. Required trial and failure of high intensity statin for a minimum of 8 week duration. Updated renewal criteria to assess overall reduction in LDL rather than specific percent reduction.	
Previous review	11/2017
Removed triple step therapy with an additional LDL lowering agent. Increased initial authorization to 6 months.	02/2016
Criteria created	08/2015

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP235

Description

Pegcetacoplan (Empaveli) is a subcutaneous complement inhibitor of C3. Iptacopan (Fabhalta) is an oral complement factor B inhibitor. Danicopan (Voydeya) is an oral complement factor D inhibitor.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
danicopan (Voydeya)	Extravascular hemolysis (EVH) in paroxysmal nocturnal hemoglobinuria (PNH)	50 mg/100 mg tablets dose pack	180 tablets/30 days
		100 mg tablets	180 tablets/30 days
pegcetacoplan (Empaveli)	Paroxysmal nocturnal hemoglobinuria (PNH)	1,080 mg/20 mL vial	160 mL (8 vials)/28 days
iptacopan (Fabhalta)	Paroxysmal nocturnal hemoglobinuria (PNH)	200 mg capsules	60 capsules/30 days
	Reduction of proteinuria in primary IgA nephropathy (IgAN) at risk of rapid disease progression	200 mg capsules	60 capsules/30 days

Initial Evaluation

- I. **Pegcetacoplan (Empaveli), iptacopan (Fabhalta), and daniopan (Voydeya)** may be considered medically necessary when the following criteria are met:
 - A. Member is 18 years of age or older; **AND**
 - B. Medication is prescribed by, or in consultation with, a hematologist or immunologist; **AND**
 - C. Provider attestation of a diagnosis of **paroxysmal nocturnal hemoglobinuria (PNH)** confirmed via flow cytometry with PNH clones of at least 10%; **AND**
 - D. The request is for **pegcetacoplan (Empaveli)** or **iptacopan (Fabhalta)**; **AND**
 1. Member has at least one of the following indications for treatment:
 - i. Transfusion dependence (hemoglobin is 7 g/dL or less)
 - ii. Hemoglobin is 9 g/dL or less with symptoms of anemia (e.g. disabling fatigue)
 - iii. The member has experienced a thromboembolic event
 - iv. Presence of organ damage secondary to chronic hemolysis (e.g., renal insufficiency, pulmonary insufficiency/hypertension)
 - v. High LDH activity ($\geq 1.5 \times$ ULN) with clinical symptoms
 - vi. Patient has symptoms associated with smooth muscle dystonia (e.g., abdominal pain, dysphagia, esophageal spasm, erectile dysfunction); **AND**
 2. The request is for pegcetacoplan (Empaveli); **OR**

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3. The request is for iptacopan (Fabhalta); **AND**
 - i. Documentation that treatment with pegcetacoplan (Empaveli) has been ineffective, contraindicated, or not tolerated; **AND**
 4. Provider attestation that medication will not be used in combination with other complement inhibitor therapy (e.g., eculizumab [Soliris], ravulizumab [Ultomiris], danicopan [Voydeya]); **OR**
 - E. The request is for **danicopan (Voydeya)**; **AND**
 1. Member has been established on therapy with a complement component factor 5 (C5) inhibitor (e.g., eculizumab [Soliris], ravulizumab [Ultomiris]) at therapeutic maintenance doses; **AND**
 2. Documentation of persistent anemia consistent with **extravascular hemolysis (EVH) in paroxysmal nocturnal hemoglobinuria (PNH) [PNH-EVH]** defined by all the following:
 - i. Hemoglobin ≤ 9.5 g/dL
 - ii. Absolute reticulocyte count $\geq 120 \times 10^9/L$; **AND**
 3. Medication will be used in combination with a complement component 5 (C5) inhibitor (e.g., eculizumab [Soliris], ravulizumab [Ultomiris])
- II. **Iptacopan (Fabhalta)** may be considered medically necessary when the following criteria are met:
- A. Member is 18 years of age or older; **AND**
 - B. Medication is prescribed by, or in consultation with, a nephrologist or immunologist; **AND**
 - C. A diagnosis of **Primary immunoglobulin A nephropathy (IgAN)** when the following are met:
 1. Diagnosis of Primary immunoglobulin A nephropathy (IgAN) has been confirmed by a kidney biopsy; **AND**
 2. Documentation of elevated protein levels in urine as indicated by proteinuria ≥ 1 g/day or urine protein to creatinine ratio (UPCR) ≥ 1.5 g/g; **AND**
 3. Member is not currently receiving dialysis and has not undergone kidney transplant; **AND**
 4. Treatment with a renin-angiotensin system (RAS) inhibitor for ≥ 3 months [e.g., angiotensin converting enzyme (ACE) inhibitor (e.g., enalapril, lisinopril); angiotensin receptor blocker (ARB) (e.g., valsartan, irbesartan)] has been ineffective, not tolerated, or all are contraindicated; **AND**
 - D. Treatment will not be used in combination with atrasentan (Vanrafia), budesonide (Tarpeyo), or sparsentan (Filspari)
- III. Pegcetacoplan (Empaveli), iptacopan (Fabhalta), and danicopan (Voydeya) are considered investigational when used for all other conditions, including but not limited to:
- A. Paroxysmal nocturnal hemoglobinuria in pediatric patients
 - B. Paroxysmal nocturnal hemoglobinuria in combination with other complement inhibitors [with the exception of danicopan (Voydeya) in combination with C5 inhibitors]
 - C. Amyotrophic lateral sclerosis (ALS)
 - D. Macular degeneration

- E. Hemolytic uremic syndrome
- F. Myasthenia gravis
- G. Neuromyelitis optica spectrum disorder (NMOSD)
- H. Thrombotic microangiopathy
- I. Immune thrombocytopenia
- J. Immunoglobulin A (IgA) vasculitis (Henoch-Schoenlein purpura) in pediatric patients
- K. Geographic atrophy (GA) secondary to age-related macular degeneration
- L. Secondary IgA nephropathy

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. The member has a diagnosis of **Primary immunoglobulin A nephropathy (IgAN); AND**
 - A. The request is for iptacopan (Fabhalta); **AND**
 - i. Member is not currently receiving dialysis and has not undergone kidney transplant; **AND**
 - ii. Treatment will not be used in combination with atrasentan (Vanrafia), budesonide (Tarpeyo), or sparsentan (Filspari); **AND**
 - iii. Member has exhibited improvement or stability of disease symptoms (e.g., reduction in proteinuria <1 g/day or urine protein to creatinine ratio (UPCR) < 1.5 g/g); **OR**
- IV. The member has a diagnosis of **Paroxysmal nocturnal hemoglobinuria (PNH); AND**
 - A. Member has exhibited improvement or stability of disease symptoms (e.g., increased hemoglobin, reduction in LDH, reduction in reticulocyte count, reduction in transfusion frequency); **AND**
 - B. For **pegcetacoplan (Empaveli) or iptacopan (Fabhalta)**:
 - i. Provider attestation that medication will not be used in combination with other complement inhibitor therapy (e.g., eculizumab [Soliris], ravulizumab [Ultomiris], danicopan [Voydeya]); **OR**
 - C. For **danicopan (Voydeya)**:
 - i. The medication will be used in combination with a C5 inhibitor (e.g., eculizumab [Soliris], ravulizumab [Ultomiris])

Supporting Evidence

Paroxysmal nocturnal hemoglobinuria (PNH)

- I. Paroxysmal nocturnal hemoglobinuria (PNH) is a rare disease characterized by complement-mediated hemolysis, leading to debilitating fatigue, anemia, dyspnea, bone pain, bleeding/bruising, thrombosis, and bone marrow dysfunction. Curative therapy for PNH is allogeneic hematopoietic stem cell (HSC) transplant; however, given safety and cost limitations, transplant is reserved for those with severe and refractory disease manifestations.

- II. Diagnosis and treatment of this condition is highly specialized. To ensure an appropriate diagnosis and that the benefits of treatment outweigh the risks, prescribing by, or in consultation with, a specialist is required. Confirmation of diagnosis by Flow Cytometry is currently the most accepted method to confirm diagnosis of PNH. Therefore, this is required given the rarity of PNH and to ensure medication is medically necessary as the proportion of PNH III cells, which are cells completely missing GPI-anchored proteins on the cell surface, can be diluted by a recent transfusion or depleted due to a recent hemolytic crisis.
- III. Pegcetacoplan (Empaveli) and iptacopan (Fabhalta) have not been evaluated in combination with other complement inhibitors. There is currently one open-label, single-arm, Phase 2 trial that is evaluating the use of iptacopan (Fabhalta) and eculizumab (Soliris) combination use; however, study results are not mature. Therefore, the efficacy and safety of combination use remains unknown at this time.
- IV. Treatment for PNH is indicated when signs and symptoms are present with a diagnosis confirmed via flow cytometry. Signs and symptoms include transfusion dependence (defined as a Hgb ≤ 7 g/dL), symptoms of anemia with a Hgb ≤ 9 g/dL, thrombosis, organ dysfunction, and debilitating fatigue associated with hematologic lab values that are out of the normal range (e.g., low Hgb, increased LDH, etc.). Smooth muscle dystonia can occur due to hemolysis induced depletion of nitric oxide, and is associated with abdominal pain, dysphagia, erectile dysfunction, and esophageal spasm. Nitric oxide depletion or pulmonary emboli can also be associated with pulmonary hypertension in some patients. The chronic hemolysis and associated anemia experienced by PNH patients can lead to disabling fatigue along with acute and chronic kidney disease. Anemia, and therefore the need for transfusions, can be multifactorial with hemolysis, iron deficiency, and bone marrow failure, all of which contribute to low Hgb levels. The increased risk of thrombosis in PNH has a variety of potential contributing factors to the hypercoagulability state including prothrombotic microparticles, high levels of free Hgb, complement activation, and the absence/deficiency of GPI-linked proteins.
- V. The C5 inhibitors, eculizumab (Soliris) and ravulizumab (Ultomiris) ($\pm$ supportive care), have become standard of care given their ability to improve disease manifestations. However, these only target intravascular hemolysis, leaving opportunity for extravascular hemolysis in the liver and spleen. Despite treatment, anemia and the need for continued blood transfusions may persist in some patients. For the majority of patients C5 inhibitors are successful treatment options as they have been shown to improve Hg, LDH levels, reticulocyte count, and/or reduce transfusion frequency. The safety profile of these therapies is well established.
- VI. **Pegcetacoplan (Empaveli)**
 - Pegcetacoplan (Empaveli) is a C3 complement inhibitor and acts proximally to the complement cascade preventing intravascular and extravascular hemolysis. It is the first complement inhibitor that may be self-administered via a subcutaneous infusion pump; although, therapy may also be administered by a healthcare provider.
 - To date, pegcetacoplan (Empaveli) has been evaluated in adult patients. Clinical trials are underway to evaluate the safety and efficacy of pediatric patients. However, other therapies [e.g., ravulizumab (Ultomiris)] have been evaluated and are FDA-approved down to one month of age. Until sufficiently evaluated in pediatric patients, pegcetacoplan (Empaveli) should be reserved for the FDA-approved age group(s) given the availability of alternate avenues of care (e.g., other FDA-approved medications, enrolment in clinical trials).
 - The pivotal trial for pegcetacoplan (Empaveli) was an open label, randomized, Phase 3 study in comparison to eculizumab (Soliris) (PEGASUS trial). Patients were 18 years of age or older, had a hemoglobin of less than 10.5 mg/dL (mean 8.7 g/dL) while on stable

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doses of eculizumab (Soliris) for at least three months before enrollment, 75% received a blood transfusion in the last year (over 50% of patients received four or more).

- Eighty patients were enrolled in the trial. Seventy-five percent had received a blood transfusion in the last year (over 50% of patients received four or more). Primary outcome: change in Hg from baseline at week 16. Secondary outcomes: proportion of transfusion-free patients, change in reticulocyte count, lactate dehydrogenase (LDH) level, and Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F). The normalization of hematologic variables was also evaluated. Endpoints were tested in a hierarchical manner, the primary outcome was tested for superiority, and the secondary outcomes were tested for non-inferiority (NI). The primary outcome met superiority, and transfusion rate and reticulocyte count met NI. Normalization of hematologic variables (Hg, reticulocytes, LDH) were favorable for pegcetacoplan (Empaveli). Pegcetacoplan (Empaveli) was also evaluated in Phase 1 and 2 open-label, single-arm trials in complement inhibitor-naïve patients. Improvements were seen in Hg, LDH, reticulocytes, and FACIT-F scores in a small number of patients.
- The safety and efficacy of pegcetacoplan (Empaveli) has been established for 1,080 mg (20 mL) twice weekly. In the clinical trials, three patients discontinued therapy given lack of efficacy, following this, a protocol amendment was made to allow an increase in the dose to every three days, and two patients received the increased dose. Data regarding the safety and efficacy of 1,080 mg (20mL) three times a week has been proven in scientific literature, and the pegcetacoplan (Empaveli) prescribing information recommends adjusting the dosing to 1,080mg (20 mL) every three days for lactate dehydrogenase (LDH) levels greater than 2× the upper limit of normal (ULN).
- With the exception of the four-week overlap to get patients established on pegcetacoplan (Empaveli), therapy has not been evaluated in combination with other complement inhibitors. It is advised that complement inhibitors are not abruptly discontinued. If switching from eculizumab (Soliris), therapy should be overlapped for four weeks with pegcetacoplan (Empaveli). For those switching from ravulizumab (Ultomiris), pegcetacoplan (Empaveli) should be started no more than four weeks after the last dose of ravulizumab (Ultomiris). Maintenance therapy with more than one complement inhibitor therapy is not expected to have additional efficacy and is expected to have serious safety implications (e.g., serious infections caused by encapsulated bacteria). Thus, maintenance on more than one complement inhibitor therapy is not indicated at this time.
- The bulk of evidence is from patients that were refractory to the C5 inhibitor eculizumab (Soliris), and it is expected that pegcetacoplan (Empaveli) will be utilized heavily in this treatment setting; however, given the alternative protein target of this therapy, coupled with evidence data support from Phase 1 and 2 trials, it is expected pegcetacoplan (Empaveli) will be efficacious as a first-line treatment. A clinical trial is underway to evaluate this further.

VII. Iptacopan (Fabhalta)

- The safety and efficacy of iptacopan (Fabhalta) was evaluated in two Phase 3, multicenter, open-label trials. Both trials were studied in adult patients aged 18 years and older. Safety and efficacy have not been evaluated for pediatric patients.
- The APPPLY-PNH trial was a 24-week multicenter, open-label, randomized, Phase 3 trial which compared iptacopan (Fabhalta) against standard of care (SOC) eculizumab (Soliris) or ravulizumab (Ultomiris) in adult patients with PNH, as evidenced by a diagnosis via

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high-sensitivity flow cytometry with a clone size $\geq 10\%$ and a hemoglobin less than 10 g/dL. Patients were required to be on a stable dose of eculizumab (Soliris) or ravulizumab (Ultomiris) for at least 6 months prior to randomization and 56% of patients had received a blood transfusion in the 6 months prior to enrollment. The primary endpoint was the percentage of participants achieving a hematological response, defined as an increase from baseline in Hb ≥ 2 g/dL in the absence of RBC transfusions, and demonstrated statistically significant change compared to SOC (difference: 80.3% [95% CI: 71.3-87.6]; $p < 0.0001$). The other primary endpoint, percentage of participants achieving sustained Hb ≥ 12 g/dL in the absence of RBC transfusions, also demonstrated statistical significance compared to SOC (difference: 67.0% [95% CI: 56.3-76.9]; $p < 0.0001$).

- The APPOINT-PNH trial was an open-label, single arm, Phase 3 trial that enrolled 40 treatment naïve, adult patients with a high-sensitivity flow cytometry clone size of $\geq 10\%$, Hgb < 10 g/dL, and a LDH > 1.5 ULN. The primary endpoint, percentage achieving hematological response, defined as an increase from baseline in Hb ≥ 2 g/dL in the absence of red blood cell (RBC) transfusions, was met (92.2% (95% CI: 82.5-100)). One key secondary endpoint was percentage achieving hematological response defined as having Hb ≥ 12 g/dL in the absence of RBC transfusions, which was also met (62.8% (95% CI: 47.5-77.5)).
- The safety and efficacy of iptacopan (Fabhalta) has been established for the 200mg capsules twice daily. In the APPLY trial 82.3% of patients experienced a treatment emergent adverse event (TEAE) as compared to 80% of the comparator group. The most common TEAEs in the iptacopan (Fabhalta) group were headache (16.1%), diarrhea (14.5%), and nasopharyngitis (11.3%). Serious TEAEs occurred in 9.7% of the iptacopan (Fabhalta) patients while 14.3% of patients in the comparator group experienced a serious TEAE. No patient in the iptacopan (Fabhalta) group experienced a hemolysis related serious TEAE while one patient in the comparator group experienced breakthrough hemolysis and another experienced extravascular hemolysis. No patients discontinued due to adverse events or deaths. In the APPOINT trial, no breakthrough hemolysis events, or major adverse vascular events (MAVEs) were reported during the 24-week core treatment period. Treatment emergent adverse events (TEAEs) were reported in 93% of patients with 65% considered mild in severity. The most common TEAEs were headache (27.5%), COVID-19 (15%), and upper respiratory tract infection (12.5%). Serious TEAEs were reported in 10% of patients with one case of bacterial pneumonia, COVID-19, type II diabetes mellitus, and cataract. No patients discontinued due to side effects and no deaths were reported.

VIII. Both iptacopan (Fabhalta) and pegcetacoplan (Empaveli) have studies (APPLY-PNH and PEGASUS, respectively) demonstrating their efficacy in patients who were not clinically stable on anti-C5 therapy. There are no direct comparison trials available demonstrating superiority of iptacopan (Fabhalta) to pegcetacoplan (Empaveli), the use of the most cost-effective treatment option should be considered. For these reasons, trial of pegcetacoplan (Empaveli) is required prior to use of iptacopan (Fabhalta), unless contraindicated, not tolerated, or ineffective.

IX. **Danicopan (Voydeya)**

- Danicopan (Voydeya) is a complement factor D inhibitor FDA-approved to treat extravascular hemolysis (EVH) symptoms in patients with an incomplete response to C5 inhibitors [eculizumab (Soliris) or ravulizumab (Ultomiris)] at maintenance doses. Paroxysmal nocturnal hemoglobinuria with extravascular hemolysis (PNH-EVH) occurs in roughly 10-20% of patients with PNH and is the result of uncontrolled accumulation of

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C3 which targets RBC in the spleen and liver. Clinically evident EVH presents as symptomatic anemia, increased reticulocytes and LDH $\geq 1.5 \times \text{ULN}$ in the absence of other causes of anemia (e.g., folate deficiency, bleeding). Paroxysmal nocturnal hemoglobinuria with extravascular hemolysis (PNH-EVH) may limit the hematologic benefits of C5 inhibitors, resulting in symptomatic anemia, transfusion dependency, and fatigue. It does not affect mortality or risk of thrombosis, but it does negatively affect quality of life.

- Danicopan (Voydeya) was studied in a 12-week, Phase 3, randomized, double-blind, placebo-controlled clinical trial (ALPHA) in 73 adult patients with PNH, who were stable on C5 inhibitor therapy for at least six months prior to enrollment and experiencing EVH, defined as hemoglobin(Hgb) ≤ 9.5 g/dL with absolute reticulocyte count $\geq 120 \times 10^9/\text{L}$. Patients received danicopan (Voydeya) (n=49) or placebo (n=24) orally three times a day in addition to C5 background therapy [eculizumab (Soliris) or ravulizumab (Ultomiris)]. Sixty-three patients were included in the primary statistical analysis; all 73 were included in the safety outcomes.
- The primary endpoint was the change in hemoglobin (Hgb) from baseline to the end of week 12 in the primary efficacy set [the first 63 patients on danicopan (Voydeya)]. The primary endpoint met statistical significance with a mean change in Hgb from baseline of 2.94 g/dL in the danicopan (Voydeya) arm and 0.50 g/dL in the placebo arm; a difference of 2.44 g/dL (1.69-3.20; $p < 0.001$). Secondary endpoints including percentage of participants achieving ≥ 2 g/dL Hgb increase, transfusion avoidance, mean change in the FACIT-fatigue scores, and absolute reticulocyte counts were also met, achieving statistically significant results compared to placebo. A 12-week extension of ALPHA and an additional ongoing two-year open label period, where all patients on placebo changed to receiving danicopan (Voydeya) in addition to C5 therapy, demonstrated sustained benefit in the endpoints through the reported 48-weeks of data.
- Danicopan (Voydeya) was well tolerated with the most commonly reported TEAE as headaches (11%). Other commonly reported AEs occurring over 5% of the 73 danicopan (Voydeya) treated patients included vomiting, pyrexia, and increase in serum triglycerides. No deaths occurred in the study. Danicopan (Voydeya) also includes the same REMS program as the other complement factors due to risk of infections caused by encapsulated bacteria.
- The quality of evidence is moderate considering this was a well-designed randomized, placebo, controlled, Phase 3 clinical trial that demonstrated statistically significant and clinically meaningful changes in the primary and secondary endpoints. These endpoints portray symptom relief, better functioning, and greater health-related quality of life assessments in PNH patients who are experiencing EVH and are not adequately controlled on a C5 inhibitor therapy.
- The dosing of danicopan (Voydeya) is 150 mg three times a day and can be increased to 200 mg three times a day if the patients' Hgb has not increased by 2 g/dL in four weeks. During the clinical trial, 44 patients (60.3%) required increasing to 200 mg to achieve the 2 g/dL increase.

Primary Immunoglobulin A Nephropathy (IgAN)

- I. Primary Immunoglobulin A Nephropathy (IgAN), also called Berger's disease, is a rare kidney disorder characterized by deposits of immune complexes containing galactose-deficient IgA in the glomerular mesangium leading to glomerulosclerosis, and renal failure. Although previously

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considered a benign condition, IgAN is now recognized to cause end-stage renal disease (ESRD) in 30% of affected individuals.

- II. The Kidney Disease Improving Global Outcomes (KDIGO) guideline indicates IgAN can only be diagnosed with a kidney biopsy. While there are several prognostic scoring tools that have been developed to assist in predicting kidney outcomes of IgAN patients (i.e., MEST-C, International IgAN Prediction Tool, etc.) there are currently no validated diagnostic serum or urine biomarkers.
- III. Due to the complexities related to diagnosis monitoring and management of IgAN patients, therapy for this disease space should be initiated by or in consultation with a specialist such as nephrologist or immunologist.
- IV. There are no curative therapies for IgAN. Supportive care with blood pressure management, use of renin-angiotensin system (RAS) blockers (ACEis or ARBs), and lifestyle modifications are the recommended initial interventions for IgAN treatment. Patients with proteinuria level of ≥ 1 g/day (or urine protein to creatinine ratio (UPCR) > 1.5 g/g) despite 3 to 6 months of initial treatment, are at high risk of progression to kidney failure. The Kidney Disease Improving Global Outcomes guideline for the management of glomerular diseases strongly recommends proteinuria reduction < 1 g/day as a treatment goal for high-risk IgAN.
- V. As of July 2025, there are four therapies approved for the treatment of IgAN via the FDA's accelerated approval pathway: budesonide (Tarpeyo), sparsentan (Filspari), iptacopan (Fabhalta), and atrasentan (Vanrafia). Tarpeyo and Filspari have received full FDA-approval based on positive clinical response based on reduced proteinuria and long-term kidney data. Continued approval of Fabhalta and Vanrafia will be contingent on confirmation of a clinical benefit is expected later 2025 and early 2026.
- VI. The accelerated approval for iptacopan (Fabhalta) for the treatment of the IgAN indication was based on the Phase 3 randomized, double-blind APPLAUSE-IgAN trial (NCT04578834). The study enrolled adults with biopsy-proven IgAN ($\text{eGFR} \geq 20$ mL/min/1.73m², and UPCR ≥ 1 g/g on a stable dose of maximally-tolerated RAS inhibitor therapy with or without a stable dose of a sodium-glucose cotransporter-2 [SGLT2] inhibitor). The trial excluded participants on chronic dialysis or kidney transplantation for end-stage kidney disease as these are considered clinical outcomes of interest. The interim efficacy analysis was based on the first 250 patients with $\text{eGFR} \geq 30$ mL/min/1.73 m² who had completed or discontinued the study prior to the month 9 visit. The two primary endpoints of the study for the interim and final analysis, respectively, are proteinuria reduction at 9 months as measured by 24-hour UPCR, and the annualized total eGFR slope over 24 months. Patients receiving iptacopan (Fabhalta) had a proteinuria reduction of 44% compared with 9% in the placebo group at 9 months, translating to a clinically significant 38% reduction for iptacopan (Fabhalta) versus placebo. Moreover, the benefit remained consistent across all subgroups, including those with SGLT2 inhibitor use.
- VII. The most common adverse reactions in adults with IgAN were upper respiratory tract infection (9%), lipid disorder (6%), and abdominal pain (6%). Iptacopan (Fabhalta) label carries the same risks and precautions as it does for PNG. The label for iptacopan (Fabhalta) includes a Boxed Warning regarding an increased risk for serious and life-threatening infections caused by encapsulated bacteria, including *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* type B. Due to this risk, iptacopan (Fabhalta) is only available through a Risk Evaluation and Mitigation Strategies (REMS) program. Vaccination against encapsulated bacteria or antibacterial drug prophylaxis (in patients who are not up to date with vaccines) is

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recommended. Iptacopan (Fabhalta) is contraindicated in individuals with unresolved serious infections.

- VIII. The quality of evidence for iptacopan (Fabhalta) is considered low. The APPLAUSE-IgAN clinical program consists of an ongoing trial, alluding to a short-term indication of efficacy. Reduction in proteinuria < 1 g/day is an objective surrogate marker for IgAN. However, it falls shy of predicting long-term patient outcomes such as progression to ESRD, dialysis dependence and overall mortality in ESRD. The Kidney Health Initiating workgroup and National Kidney Foundation recommend the use of dual (primary and confirmatory) endpoints of proteinuria reduction as well as slope of eGFR decline. At this time, effect of iptacopan (Fabhalta) on eGFR is unknown compared to other agents on the market. Currently, all four approved therapies for IgAN demonstrate comparable reductions in UPCR; but ultimately, confirmatory eGFR data from both iptacopan (Fabhalta) and atrasentan (Vanrafia) will be essential for evaluating their impact on long term kidney function.
- IX. As of July 2025, no clinical trials support the combined use of multiple novel therapies in IgAN. While it is known that multiple pathophysiologic mechanisms contribute to kidney function loss in patients with IgAN, particularly those at risk of progressive decline, targeting these mechanisms concurrently may be necessary. In clinical practice, this could mean combining standard of care therapies with one or more agents. In the absence of updated clinical guidelines and supporting evidence to allow combination use of IgAN therapies (e.g., atrasentan (Vanrafia), budesonide (Tarpeyo), sparsentan (Filspari), iptacopan (Fabhalta), etc.), concurrent use is contraindicated and considered experimental and investigational.

Investigational or Not Medically Necessary Uses

- I. Pegcetacoplan (Empaveli), iptacopan (Fabhalta), and danicopan (Voydeya) have not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
- A. Paroxysmal nocturnal hemoglobinuria in pediatric patients
 - B. Paroxysmal nocturnal hemoglobinuria in combination with other complement inhibitors [with the exception of danicopan (Voydeya) in combination with C5 inhibitors]
 - C. Amyotrophic lateral sclerosis (ALS)
 - D. Macular degeneration
 - E. Hemolytic uremic syndrome
 - F. Myasthenia gravis
 - G. Neuromyelitis optica spectrum disorder
 - H. Thrombotic microangiopathy
 - I. Immune thrombocytopenia
 - J. Immunoglobulin A (IgA) vasculitis (Henoch-Schoenlein purpura) in pediatric patients
 - K. Geographic atrophy (GA) secondary to age-related macular degeneration
 - L. Secondary IgA nephropathy

Appendix

I. Complement inhibitor administration for PNH:

Therapy	Dose/Frequency	Duration of medication coverage (maintenance)	Route
iptacopan (Fabhalta)	200 mg twice daily	1 day	PO
pegcetacoplan (Empaveli)	1,080 mg (20 mL) twice weekly	3-4 days	SQ
eculizumab (Soliris)	Loading dose: 600 mg weekly for four weeks, 900 mg on the fifth week Maintenance, therapeutic dosing: 900 mg every two weeks thereafter	2 weeks	IV
ravulizumab (Ultomiris)	One loading dose (based on weight) 2,400 mg-3,000 mg, then maintenance treatment/therapeutic dosing (based on weight) starting two weeks later: 3,000 mg – 3,600 mg every eight weeks	8 weeks	IV
danicopan (Voydeya)	Start 150 mg three times a day orally, with or without food. Depending on clinical response, can increase to 200 mg three times a day.	1 day	PO

II. Switch therapy guidance for PNH:

- Transitioning from eculizumab (Soliris) to pegcetacoplan (Empaveli): Overlap therapy for four weeks (i.e., initiate pegcetacoplan [Empaveli] while continuing eculizumab [Soliris] at the current dose). Then, discontinue eculizumab (Soliris) after four weeks of treatment with pegcetacoplan (Empaveli) - to utilize pegcetacoplan (Empaveli) as monotherapy.
- Transitioning from ravulizumab (Ultomiris) to pegcetacoplan (Empaveli): Once the last dose of ravulizumab (Ultomiris) is administered, pegcetacoplan (Empaveli) should be initiated within four weeks of the infusion. No further doses of ravulizumab (Ultomiris) should be administered while pegcetacoplan (Empaveli) treatment is active.
- Transitioning from eculizumab (Soliris) to iptacopan (Fabhalta): initiate iptacopan (Fabhalta) no later than one week after the last dose of eculizumab (Soliris).
- Transitioning from ravulizumab (Ultomiris) to iptacopan (Fabhalta): initiate iptacopan (Fabhalta) no later than 6 weeks after the last dose of ravulizumab (Ultomiris).
- Transitioning from eculizumab (Soliris) to ravulizumab (Ultomiris) or vice versa: reference prescribing information for guidance.

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
Budesonide (Tarpeyo)	Primary IgA nephropathy; at high risk of progression
Sparsentan (Filspari) and atrasentan (Vanrafia)	Primary IgA nephropathy; at high risk of progression

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated policy name from “Paroxysmal Nocturnal Hemoglobinuria Agents” to “Proximal Complement Inhibitors.” Added pathway to coverage for iptacopan (Fabhalta) for the treatment of primary IgAN. Updated supporting evidence, E/I, references. Added related policies.	07/2025
Added danicopan (Voydeya) tablets to the policy. Updated supporting evidence.	08/2024
Added iptacopan (Fabhalta) capsules to the policy. Updated supporting evidence and other investigational conditions.	02/2024
Policy created	08/2021

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP145

Description

Ambrisentan (generic, Letairis®), bosentan (generic, Tracleer®), and macitentan (Opsumit®) are endothelin receptor agonists (ERA) that inhibit the binding of endothelin – a vasoconstrictive peptide – to its receptors (ETA and ETB) in the endothelium and smooth muscle cells which results in vasodilation.

Tadalafil/macitentan (Opsnvi) is a combination product consisting of a phosphodiesterase type 5 (PDE5) inhibitor and an endothelin receptor agonist (ERA).

Riociguat (Adempas®) stimulates soluble guanylate cyclase (sGC) – a receptor for nitric oxide and an enzyme in the cardiopulmonary system. It sensitizes sGC to endogenous nitric oxide by stabilizing nitric oxide-sGC binding and directly stimulating sGC via a different binding site. Stimulating the nitric oxide-sGC-cGMP pathway, leads to an increased generation of cGMP and subsequent vasodilation.

Iloprost (Ventavis®) inhalation solution, treprostinil (Tyvaso®) inhalation solution, treprostinil (Orenitram®) tablets for oral use, treprostinil (Remodulin®) injection for subcutaneous use and selexipag (Uptravi®) tablets for oral use are prostacyclin vasodilators. They directly vasodilate pulmonary and systemic arterial vascular beds, inhibit platelet aggregation, and inhibit smooth muscle cell proliferation.

Sotatercept (Winreviar) is an activin signaling inhibitor that binds to Activin A and other TGF-β superfamily ligands, which improves the balance between the pro-proliferative and anti-proliferative signaling to modulate vascular proliferation.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
ambrisentan (Letairis)	Pulmonary arterial hypertension (PAH)	5 mg tablets	30 tablets/30 days
		10 mg tablets	
generic ambrisentan		5 mg tablets	30 tablets/30 days
		10 mg tablets	
bosentan (Tracleer)		32 mg tablet for oral suspension	120 tablets/30 days
		62.5 mg film-coated tablet	60 tablets/30 days
		125 mg film-coated tablet	
generic bosentan		32 mg tablet for oral suspension	120 tablets/30 days
		62.5 mg film-coated tablet	60 tablets/30 days
		125 mg film-coated tablet	
macitentan (Opsumit)		10 mg tablet	30 tablets/30 days
riociguat (Adempas)		0.5 mg tablets	90 tablets/30 days

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HEALTH

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	Chronic thromboembolic pulmonary hypertension (CTEPH); Pulmonary arterial hypertension (PAH)	1 mg tablets		
		1.5 mg tablets		
		2 mg tablets		
		2.5 mg tablets		
iloprost (Ventavis)	Pulmonary arterial hypertension (PAH)	10 mcg/mL inhalation solution ampule	9 cartons of 30 ampules per 30-day supply	
		20 mcg/mL inhalation solution ampule		
treprostinil (Tyvaso)	Pulmonary arterial hypertension (PAH); Pulmonary hypertension (PH) Due to Interstitial Lung Disease (ILD)	1.74 mg/2.9 mL inhalation solution ampule	1 Inhalation System Starter Kit (28 ampule carton)/ 1 st 28 days of initiation therapy 1 Inhalation System Refill Kit (28 ampule carton)/28 days 7 Four Pack Cartons with one foil pouch containing four 2.9 mL ampules/28 days	
treprostinil (Tyvaso DPI)		Maintenance Kit 16 mcg cartridge	112 cartridges/28 days	
		Maintenance Kit 32 mcg cartridge		
		Maintenance Kit 48 mcg cartridge		
		Maintenance Kit 64 mcg cartridge		
		Maintenance Kit 32 mcg & 48 mcg	224 cartridges/28 days	
		Titration Kit 16 mcg & 32 mcg	196 cartridges/28 days	
		Titration Kit 16 & 32 & 48 mcg	252 cartridges/28 days	
treprostinil (Yutrepia DPI)		Pulmonary arterial hypertension (PAH); Pulmonary hypertension associated with	26.5 mcg capsules	5 capsules/day
			53 mcg capsules	
			79.5 mcg capsules	
			106 mcg capsules	

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	Interstitial Lung Disease (ILD)		
treprostinil (Remodulin)	Pulmonary arterial hypertension (PAH)	5 mg/mL injection solution	up to 50 ng per kg per minute subcutaneously or intravenously
		10 mg/mL injection solution	
		20 mg/20 mL injection solution	
		50 mg/20 mL injection solution	
		100 mg/20 mL injection solution	
		200 mg/20 mL injection solution	
treprostinil (Orenitram)		0.125 mg ER tablet	90 extended-release oral tablets/30 days
		0.25 mg ER tablet	
		1 mg ER tablet	
		2.5 mg ER tablet	
		5 mg ER tablet	
selexipag (Uptravi)		200 mcg	140 oral use tablets/28 days
		400 mcg	Titration pack (140 count – 200mcg oral use tablets + 60 count – 800mcg)
		600 mcg	
		800 mcg	
		1000 mcg	
		1200 mcg	
		1400 mcg	
		1600 mcg	60 oral use tablets/30 days
sotatercept (Winrevair)	Pulmonary arterial hypertension (PAH)	45 mg injection kit	1 kit/21 days
		60 mg injection kit	
Macitentan/tadalafil (Opsynvi)	Pulmonary arterial hypertension (PAH)	10 mg/20 mg tablet	30 tablets/30 days
		10 mg/40 mg tablet	

Initial Evaluation

- I. **Ambrisentan (Letairis), generic ambrisentan, bosentan (Tracleer), generic bosentan, macitentan (Opsumit), macitentan/tadalafil (Opsynvi), riociguat (Adempas), iloprost (Ventavis) inhalation solution, treprostinil (Tyvaso, Tyvaso DPI), treprostinil capsule (Yutrepia), treprostinil (Orenitram), treprostinil injection (Remodulin), selexipag (Uptravi), and sotatercept (Winrevair)** may be considered medically necessary when the following criteria below are met:
 - A. Member is 18 years of age or older; **OR**
 1. Member is three years of age or older and request is for bosentan (generic, Tracleer); **AND**
 - B. Medication is prescribed by, or in consultation with, cardiologist or pulmonologist; **AND**
 - C. A diagnosis of one of the following:
 1. **Pulmonary arterial hypertension (PAH) (WHO Group 1); AND**
 - a. An acute vasoreactivity test has been performed; **AND**
 - i. Results were negative; **OR**
 - ii. Results were positive; **AND**

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1. Treatment with a calcium channel blocker (CCB) (e.g. amlodipine, diltiazem, felodipine, nifedipine, nicardipine, or verapamil) has been ineffective after three months of therapy, unless contraindicated, or not tolerated; **AND**
- b. The request is for generic ambrisentan, generic bosentan, macitentan (Opsumit), or riociguat (Adempas); **OR**
 - i. The request is for brand ambrisentan (Letairis); **AND**
 1. Generic ambrisentan has been ineffective, contraindicated, or not tolerated; **OR**
 - ii. The request is for brand bosentan (Tracleer); **AND**
 1. Generic bosentan has been ineffective, contraindicated, or not tolerated; **OR**
 - iii. The request is for macitentan/tadalafil (Opsynvi); **AND**
 1. The member has documented non-adherence to dual therapy with an ERA and a PDE-5 inhibitor (taken as individual components); **OR**
- c. The request is for iloprost (Ventavis) inhalation solution, treprostinil (Tyvaso) inhalation solution, treprostinil dry powder inhalation (Tyvaso DPI), treprostinil capsule (Yutrepia), treprostinil (Orenitram) or selexipag (Uptravi); **AND**
 - i. Treatment with TWO of the following groups has been ineffective, contraindicated, or not tolerated:
 1. Endothelin receptor antagonist [e.g., bosentan (Tracleer), ambrisentan (Letairis), or macitentan (Opsumit)]
 2. Phosphodiesterase type 5 (PDE5 inhibitor) [e.g., sildenafil, tadalafil]
 3. riociguat (Adempas); **OR**
- d. The request is for treprostinil injection solution; **AND**
 - i. The request is for the generic treprostinil injection; **OR**
 1. Request is for brand Remodulin and generic treprostinil injection solution has been ineffective, contraindicated, or not tolerated; **AND**
 - ii. Member has WHO functional class IV symptoms; **OR**
 - iii. Member has WHO functional class III symptoms and is classified as high risk (poor prognosis) [see appendix table 1]; **OR**
 1. The member has WHO functional class III symptoms and is classified as low risk (good prognosis); **AND**
 - a. Treatment with TWO of the following groups has been ineffective, contraindicated, or not tolerated:
 - i. Endothelin receptor antagonist [e.g., bosentan (Tracleer), ambrisentan (Letairis), or macitentan (Opsumit)]
 - ii. Phosphodiesterase type 5 (PDE5 inhibitor) [e.g., sildenafil, tadalafil]

- iii. riociguat (Adempas); **OR**
 - iv. Member is transitioning from epoprostenol to treprostinil (Remodulin); **OR**
 - e. The request is for sotatercept (Winrevair); **AND**
 - i. Member has WHO functional class II or III symptoms; **AND**
 - ii. Provider attestation that the member has, or will receive, training from a healthcare professional on how to reconstitute, prepare, measure, and inject sotatercept (Winrevair); **AND**
 - iii. Treatment with one agent in each of the following groups has been ineffective, contraindicated, or not tolerated:
 - 1. Endothelin receptor antagonist [e.g., bosentan (Tracleer), ambrisentan (Letairis), or macitentan (Opsumit)]
 - 2. Phosphodiesterase type 5 (PDE5 inhibitor) [e.g., sildenafil, tadalafil] or riociguat (Adempas)
 - 3. Prostacyclin agonist [e.g., treprostinil (Remodulin, Tyvaso, Orenitram), selexipeg (Uptravi)]; **AND**
 - iv. Provider attestation that the member will be continuing background therapy with at least two other PAH medications, unless contraindicated or not tolerated; **OR**
 - 2. **Persistent/recurrent Chronic Thromboembolic Pulmonary Hypertension (CTEPH) (WHO Group 4); AND**
 - i. Member has inoperable CTEPH; **OR**
 - ii. Member had a surgery for CTEPH performed; **AND**
 - iii. The request is for riociguat (Adempas); **OR**
 - 3. **Pulmonary Hypertension (PH) Due to Interstitial Lung Disease (ILD) (WHO Group 3); AND**
 - i. Diagnosis confirmed with chest high-resolution computed tomography (HRCT) imaging; **AND**
 - ii. Diagnosis confirmed with a right heart catheterization (RHC); **AND**
 - iii. Member does NOT have PH caused by obstructive lung disease (e.g., chronic obstructive pulmonary disease [COPD], bronchiectasis) or hypoxia without lung disease (e.g., high altitude, sleep-disordered breathing, obesity hypoventilation); **AND**
 - iv. The request is for treprostinil (Tyvaso) inhalation solution or treprostinil dry powder inhalation (Tyvaso DPI)
- II. Ambrisentan (Letairis) is considered investigational when used for all other conditions including but not limited to:
- A. Chronic thromboembolic pulmonary hypertension (CTEPH)
 - B. Digital ulcers in systemic sclerosis
 - C. Lowering Portal Pressure in Patients with Liver Cirrhosis
 - D. Pulmonary Hypertension Associated with Idiopathic Pulmonary Fibrosis
 - E. Sarcoidosis

- III. Bosentan (Tracleer) is considered investigational when used for all other conditions including but not limited to:
 - A. Chronic obstructive pulmonary disease - Pulmonary hypertension
 - B. Chronic thromboembolic pulmonary hypertension (CTEPH)
 - C. Digital ulcers in systemic sclerosis
 - D. Essential hypertension
 - E. Raynaud phenomenon in systemic sclerosis
 - F. Thromboembolic pulmonary hypertension, chronic
- IV. Macitentan (Opsumit) is considered investigational when used for all other conditions including but not limited to:
 - A. Chronic thromboembolic pulmonary hypertension (CTEPH)
 - B. Digital ulcers in systemic sclerosis
 - C. Glioblastoma
- V. Riociguat (Adempas) is considered investigational when used for all other conditions including but not limited to:
 - A. Systemic sclerosis-associated digital ulcers
- VI. Treprostinil (Tyvaso; Tyvaso DPI; Yutrepia) is considered investigational when used for all other conditions including but not limited to:
 - A. Pulmonary hypertension (PH) WHO Groups II-V
 - Group II - Left heart disease, including congestive heart failure (CHF)
 - Group III – Chronic obstructive pulmonary disease (COPD), bronchiectasis; Hypoxia without lung disease (e.g., high altitude, sleep-disordered breathing, obesity hypoventilation)
 - Group IV - Chronic thrombotic and/or embolic disease
 - Group V - Sarcoidosis
 - B. Chronic thromboembolic pulmonary hypertension (CTEPH)
- VII. Iloprost (Ventavis), treprostinil (Orenitram, Remodulin) and selexipag (Uptravi) are considered investigational when used for all other conditions, including but not limited to:
 - A. Pulmonary hypertension (PH) WHO Groups II-V
 - Group II - Left heart disease, including congestive heart failure (CHF)
 - Group III - Lung diseases, including chronic obstructive pulmonary disease (COPD), bronchiectasis, and idiopathic pulmonary fibrosis (IPF); Other lung disease with mixed obstruction and restriction (e.g., pulmonary fibrosis with emphysema; Hypoxia without lung disease (e.g., high altitude, sleep-disordered breathing, obesity hypoventilation)
 - Group IV - Chronic thrombotic and/or embolic disease
 - Group V – Sarcoidosis
 - B. Chronic thromboembolic pulmonary hypertension (CTEPH)
- VIII. Sotatercept (Winrevair) is considered investigational when used for all other conditions including but not limited to:
 - A. Pulmonary hypertension (PH) WHO Groups II-V
 - Group II - Left heart disease, including congestive heart failure (CHF)
 - Group III - Lung diseases, including chronic obstructive pulmonary disease (COPD), bronchiectasis, and idiopathic pulmonary fibrosis (IPF); Other lung disease with mixed

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- obstruction and restriction (e.g., pulmonary fibrosis with emphysema; Hypoxia without lung disease (e.g., high altitude, sleep-disordered breathing, obesity hypoventilation))
 - Group IV - Chronic thrombotic and/or embolic disease
 - Group V – Sarcoidosis
- B. Chronic thromboembolic pulmonary hypertension (CTEPH)
- C. Newly diagnosed PH (i.e., treatment naïve)
- D. Myeloproliferative disorders/Myelofibrosis
- E. Anemia

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Member has exhibited improvement or stability of disease symptoms (e.g. improved exercise capacity and tolerance, reduced number of hospitalizations, improvement in WHO functional class)

Supporting Evidence

- I. Patients with PH are classified into five clinical groups based on cause of PH.
 - a. Group 1: pulmonary arterial hypertension (PAH) which has several causes (e.g., inheritable causes, drugs, connective tissue disease)
 - b. Group 2: PH due to left-sided heart disease
 - c. Group 3: PH due to chronic lung disorders and hypoxemia
 - d. Group 4: PH due to pulmonary artery obstructions
 - e. Group 5: PH due to unidentified mechanisms
- II. The safety and efficacy of bosentan (Tracleer) in pediatric patients was evaluated in an open-label, uncontrolled study with 19 pediatric PAH patients aged 3 to 15 years. Patients had primary pulmonary hypertension (n = 10) or PAH related to congenital heart diseases (9 patients) and were WHO functional class II or class III at baseline. Patients were dosed with bosentan for 12 weeks. Half of the patients in each group were already being treated with intravenous epoprostenol and the dose of epoprostenol remained constant for the duration of the study. Hemodynamics were measured in 17 patients. The mean decrease in (pulmonary vascular resistance) PVR was 389 dyn·sec·cm⁻⁵, which was similar to the effect seen in adults. Hemodynamic improvements from baseline were similar with or without co-administration of epoprostenol.
 *Normal PVR value is <250 dyn·sec·cm⁻⁵, but PAH patients, depending on the severity of the disease state, have a significantly higher PVR value. A Systematic Review and Meta-Analysis of 12 studies was done and baseline PVR value of the PAH patients included in the study was 668.6±219.1 >250 dyn·sec·cm⁻⁵.
- III. Clinical studies of ambrisentan (Letairis), macitentan (Opsumit), riociguat (Adempas), iloprost (Ventavis), treprostinil (Tyvaso), treprostinil (Orenitram), and selexipag (Upravi) did not include patients younger than 18 years to determine whether they respond differently from older patients. Safety and efficacy in pediatric patients have not been established.
- IV. Pulmonary Hypertension (PH) is a progressive and life-threatening disease. The medications as well as the disease state should be managed by a specialist.

PAH

- V. The American College of Chest Physicians (CHEST) guideline for Therapy for PAH in adults suggests that patients with PAH, in the absence of contraindications, should undergo acute vasoreactivity testing using a short-acting agent at a medical center with experience in the performance and interpretation of vasoreactivity testing. Contraindications to acute vasoreactivity testing include low systemic BP, low CO, or the presence of FC IV symptoms. Patients who demonstrate acute vasoreactivity – in the absence of right-sided heart failure or contraindications to CCB therapy – according to consensus definition, should be considered candidates for a trial of therapy with an oral CCB. CCBs are considered primary therapy.
- VI. Lacking head-to-head comparisons of pharmacologic agents for the treatment of PAH, there is insufficient evidence to determine if one agent is superior to another.
- VII. Ambrisentan (Letairis), bosentan (Tracleer), macitentan (Opsumit), and tadalafil/macitentan (Opsynvi) are indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) in adults to improve exercise ability and decrease clinical worsening.
 - a. Studies with bosentan (Tracleer) establishing effectiveness included predominantly patients with WHO Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital heart disease with left-to-right shunts (18%). The primary study endpoint was 6-minute walk distance; however, symptoms and functional status was also assessed. In both trials, treatment with Tracleer resulted in a significant increase in exercise ability. The improvement in walk distance was apparent after 1 month of treatment and fully developed by about 2 months of treatment.
 - b. Ambrisentan (Letairis) and macitentan (Opsumit) effectiveness was established in a long-term study in PAH patients with predominantly WHO Functional Class II-III symptoms treated for an average of 2 years. Patients who were included in this study had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), or PAH caused by congenital heart disease with repaired shunts (8%). The primary study endpoint was a 6-minute walk distance. An increase in 6-minute walk distance was observed after 4 weeks of treatment with Letairis, with a dose-response observed after 12 weeks of treatment.
 - c. Macitentan (Opsumit) effect on progression of PAH was demonstrated in a multi-center, long-term, placebo-controlled study in 742 patients with symptomatic PAH WHO FC II-IV. The primary study endpoints were time to the first occurrence of death, a significant morbidity event (defined as atrial septostomy), lung transplantation, initiation of IV or subcutaneous (SC) prostanoids, or “other worsening of PAH” during double-blind treatment plus 7 days. Other worsening was defined as all of the following: a sustained $\geq 15\%$ decrease from baseline in 6MWD, worsening of PAH symptoms (worsening of WHO FC), and need for additional treatment for PAH. All of these other worsening events were confirmed by an independent adjudication committee, blinded to treatment allocation. Treatment with OPSUMIT 10 mg resulted in a 45% reduction in the occurrence of the primary endpoint.
 - d. Tadalafil/macitentan (Opsynvi) was studied in one Phase 3, randomized, double-blind, active controlled trial against tadalafil or macitentan as monotherapy in 187 PAH patients with WHO FC II or III symptoms. The primary endpoint was change in PVR at week 16, and a statistically significant improvement was demonstrated in the tadalafil/macitentan (Opsynvi) over both monotherapy arms. Key secondary outcome of change in 6MWD did not meet the threshold for statistical significance, and other key secondary outcomes of cardiopulmonary and cardiovascular symptom score, and

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absence of worsening in WHO FC were not able to be formally tested for statistical significance due to hierarchical testing methods. No new safety signals emerged during the clinical trial, although incidence of adverse events was higher in the tadalafil/macitentan (Opsynvi) arm; this is likely due to combination therapy, which is commonly utilized in real world clinical practice.

- i. There are no head-to-head trials comparing the safety and efficacy tadalafil/macitentan (Opsynvi) to dual combination therapy with an ERA and PDE-5 inhibitor, taken as individual components, although any differences are anticipated to be negligible. Since the main driver of transition to tadalafil/macitentan (Opsynvi) would be patient preference for a single combination tablet compared to three (or more) tablets, documented non-adherence to dual therapy regimen (taken as individual components) would be the only acceptable clinical rationale for tadalafil/macitentan (Opsynvi).
- VIII. Iloprost (Ventavis), treprostinil (Tyvaso), treprostinil (Orenitram), treprostinil (Remodulin), and selexipag (Uptravi) are synthetic analogs of prostacyclin indicated for the treatment of PAH (WHO Group 1) to improve a composite endpoint consisting of exercise tolerance, symptoms (WHO Class), and lack of deterioration. Injectable treprostinil (Remodulin) also carries FDA approval for transition from epoprostenol.
- IX. Studies in Iloprost (Ventavis) establishing effectiveness included predominately patients with WHO Functional Class III-IV symptoms, etiologies of idiopathic or heritable PAH (65%), or PAH associated with connective tissue diseases (23%). The primary efficacy endpoint was clinical response at 12 weeks with a composite endpoint defined by: improvement in exercise ability (6-minute walk test) by at least 10% versus baseline evaluated 30 minutes after dosing, improvement with at least one WHO FC versus baseline, and no death or deterioration of pulmonary hypertension. The percentage of patients who had a minimum increase of at least 10 percent in the distance walked within six minutes at week 12 was slightly, but not significantly, higher in the iloprost group than in the placebo group. The absolute change in the 6MWD was significantly larger in the iloprost group. More patients in the iloprost group than in the placebo group had an improvement in the severity of heart failure, as assessed by the WHO FC.
- X. Studies in treprostinil (Tyvaso) to establish effectiveness included predominately patients with WHO Functional Class III symptoms, etiologies of idiopathic or heritable PAH (56%), or PAH associated with connective tissue diseases (33%). While there is long-term data on use of treprostinil (Tyvaso) by other routes of administration, nearly all controlled clinical experience with inhaled treprostinil (Tyvaso) has been on a background of bosentan (Tracleer) (an endothelin receptor antagonist) or sildenafil (Revatio) (a phosphodiesterase type 5 inhibitor).
- XI. Per the package insert, the study in treprostinil (Orenitram), that established effectiveness included predominately patients with WHO functional class II-III symptoms, etiologies of idiopathic or heritable PAH (75%), or PAH associated with connective tissue disease (19%). When used as the sole vasodilator, the effect of treprostinil (Orenitram) on exercise is about 10% of the deficit, and the effect, if any, on a background of another vasodilator is probably less than this.
- XII. Treprostinil injection (Remodulin) is indicated for subcutaneous or intravenous use only as a continuous infusion. The package insert states treprostinil injection is preferably infused subcutaneously but can be administered by a central intravenous line if the subcutaneous route is not tolerated. Treprostinil can be self-administered subcutaneously by continuous infusion, via a subcutaneous catheter, using an infusion pump designed for subcutaneous drug delivery. 2019 CHEST guidelines recommend use of treprostinil injection (Remodulin) for patients with

- continued progression of their disease, and/or markers of poor clinical prognosis despite treatment with one or two classes of oral agents; or in patients with WHO functional class IV.
- XIII. The effectiveness of selexipag (Uptravi) was established in a long-term study in PAH patients with WHO Functional Class II-III symptoms. Patients had idiopathic and heritable PAH (58%), PAH associated with connective tissue disease (29%), and PAH associated with congenital heart disease with repaired shunts (10%).
 - XIV. The 2019 CHEST Therapy for Pulmonary Arterial Hypertension in Adults Update of the CHEST Guideline and Expert Panel Report suggest that parental or inhaled prostanoids not be chosen as second line agents for PAH patients with WHO FC II symptoms who have not met their treatment goals. Additionally, there is no specific third line or subsequent line PAH agent noted in the guidelines. Thus, treatment after first-line therapy remains unknown as it appears addition of any of the remaining PAH treatment groups is appropriate.
 - XV. There is a limited number of head-to-head trials amongst the different PAH pharmacological agents. Due to this, a large systematic review of phase II and III RCTs was completed to compare the effectiveness of the different agents. When focusing on oral/inhaled prostanoids, riociguat (Adempas), and selexipag (Uptravi), 11 trials were included totaling 3,040 patients. While the following were not statistically significant, when comparing oral/inhaled prostanoids to riociguat (Adempas), the oral/inhaled prostanoids were favored for efficacy in improved functional status (RR 1.24, 95% CI, 0.52-2.94) and riociguat (Adempas) was favored in reducing clinical worsening (RR 4.02, 95% CI, 0.91,17.68). When comparing riociguat (Adempas) to selexipag (Uptravi), selexipag (Uptravi) was favored in improving functional status (RR 0.91, 95% CI, 0.40-2.09) and riociguat (Adempas) was favored in reducing clinical worsening (RR 0.29, 95% CI, 0.06-1.30). When comparing riociguat (Adempas) to oral/inhaled prostanoids, riociguat (Adempas) was favored for reduced risk in all-cause mortality and PAH- related hospitalizations, and improvement in 6MWD. Again, these are indirect comparisons and none of these results were statistically significant.
 - XVI. The FDA issued a warning that the combination of riociguat (Adempas) and PDE5 inhibitors is contraindicated. This is a result of the post-trial data from the PATENT-PLUS trial that showed patients taking a PDE5i and riociguat (Adempas) results in increased rates of hypotension. Additionally, the package labeling for riociguat (Adempas) specifically lists concomitant therapy with PDE5 inhibitors is contraindicated.
 - XVII. CHEST published a 2020 expert consensus that reports that selexipag (Uptravi) may be considered for patients with idiopathic pulmonary hypertension (IPAH) who are receiving dual oral therapy with an ERA and PDE5i to continue to have FC II & III symptoms.
 - XVIII. The safety and efficacy of sotatercept (Winrevair) was studied in the Phase 3, randomized, double-blind, placebo-controlled STELLAR trial in 323 adult patients with WHO group 1 PAH with functional class (FC) II or III symptoms over a period of 24 weeks. Patients continued their stable background therapy consisting of monotherapy, dual therapy, or triple therapy with medications that were available at the time of study enrollment, depending on the patient's disease severity. Approximately 60% of patients were receiving triple therapy with an PDE-5 inhibitor, ERA, and prostacyclin agonist, with nearly 40% receiving prostacyclin infusion therapy at inclusion. The primary efficacy outcome was the change in the 6-minute walk distance (6MWD) from baseline to week 24. Key secondary endpoints consisted of a multicomponent improvement at week 24 compared to baseline, and change from baseline in pulmonary vascular resistance, NT-proBNP level, and improvement in WHO functional class at week 24. All primary and key secondary endpoints met the threshold for statistical significance compared to placebo.
 - XIX. While this was a well-designed randomized, double-blind, placebo-controlled trial with sotatercept (Winrevair) demonstrating statistical significance in the key primary and secondary

endpoints, the trial utilized a surrogate endpoint as the primary endpoint and an unvalidated key secondary endpoint (MCI) that have not been shown to correlate with impact on morbidity/mortality. However, the positive impact on WHO-FC and 6MWD may be considered clinically meaningful for patients' functionality and quality of life. Based on this information, the overall quality of evidence is considered moderate. Additionally, the trial duration was limited to 24 weeks, the durability of response in this chronic disease state remains unknown and will be realized in real-world settings.

- XX. The SOTERIA trial is an ongoing, long-term (7-year) open label follow-up study of patients who completed the initial phase 2 PULSAR or Phase 3 STELLAR clinical trial; all patients were continued or were initiated on sotatercept (Winrevair), if they were originally in the placebo arm. The interim one-year follow-up data suggests that there may be maintenance benefit in the 6MWD, NT-proBNP, and WHO-FC compared with study baseline, although there was a large variance around the mean for the 6MWD and NT-proBNP outcomes. Final readout of this data is anticipated around September 2027.
- XXI. Most of the adverse events reported during the clinical trial were mild to moderate in severity, and fewer patients in the sotatercept (Winrevair) group (8.0%) experienced severe adverse events (AEs) compared to placebo (13.1%). The most common AEs reported during the clinical trial period for sotatercept (Winrevair) versus placebo, respectively, included thrombocytopenia (6.1% vs. 2.5%), bleeding events (21.5% vs. 12.5%), headache (20.2% vs. 15%), nausea (9.8% vs. 11.2%), telangiectasia (10.4% vs. 3.1%), and dizziness (10.4% vs. 1.9%). A total of nine patients died through the data cut-off date: two patients (1.2%) in the sotatercept group due to acute myocardial infarction and intracranial hemorrhage, and seven patients (4.4%) in the placebo group due to cardiac arrest, cardiogenic shock, right ventricular failure, sepsis, PAH, and COVID.
- XXII. The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines indicate oral ERA or PDE-5 inhibitor therapy as first line treatment for lower risk PAH patients. There is insufficient safety and efficacy evidence to establish that any one oral therapy for PAH is clearly superior to another. Treatment guidelines support combination therapy of PDE, ERA, and prostanoid agents.
- XXIII. For patients with WHO functional class II or III 2019 American College of Chest Physicians (CHEST) guidelines recommend the combination of ambrisentan and tadalafil as first line therapy. This is based on data from the AMBITION trial. The trial involved 605 patients with WHO functional class II or III PAH. Patients were randomly assigned to receive once daily ambrisentan plus tadalafil or to either drug alone. Doses were titrated from 5-10 mg/day for ambrisentan and from 20-40 mg/day for tadalafil. Treatment with the combination was associated with an approximately 50% reduction in risk for clinical failure compared with either drug alone ($P = .0002$), with improved exercise ability as well as decreased disease progression and hospitalization.
- XXIV. The 2019 CHEST guidelines recommend treatment naive PAH patients with WHO functional class II and III use combination therapy with ambrisentan and tadalafil to improve 6MWD. For patients who are unwilling or unable to tolerate combination therapy monotherapy with a currently approved ERA, PDE-5 inhibitor, or the soluble guanylate cyclase stimulator riociguat is advised. Guidelines suggest that parenteral or inhaled prostanoids may be chosen as initial therapy, in combination with tadalafil and ambrisentan, for treatment naive PAH patients with WHO FC III symptoms who present with a more severe phenotype, or as second line agents for PAH patients with WHO FC II symptoms who have not met their treatment goals on established dual therapy.

CTEPH

- XXV. Riociguat (Adempas) is a soluble guanylate cyclase (sGC) stimulator indicated for the treatment of adults with persistent/recurrent Chronic Thromboembolic Pulmonary Hypertension (CTEPH) after surgical treatment, inoperable CTEPH or PAH to improve exercise capacity and WHO functional class. Medical therapy prior to surgery is not indicated because there is no evidence to show it improves hemodynamic or mortality outcomes after surgery.

PH due to ILD

- XXVI. WHO Group 3 PH can be further broken down to specific causes. Those causes are:
- Obstructive lung disease (e.g., COPD or bronchiectasis)
 - Restrictive lung disease (e.g., ILD, kyphoscoliosis)
 - Other lung disease with mixed obstruction and restriction (eg, pulmonary fibrosis with emphysema)
 - Hypoxia without lung disease (e.g., high altitude, sleep apnea, obesity hypoventilation)
 - Developmental lung disorders (e.g., bronchopulmonary dysplasia, congenital lobar emphysema)
- XXVII. FDA approval for treprostinil (Tyvaso) is specific to PH associated with ILD as that was the population evaluated in clinical trials.
- XXVIII. The safety and efficacy of treprostinil (Tyvaso) inhalation solution for the treatment of patients with PH due to ILD was studied in a Phase 2/3, multicenter, randomized, double-blinded, placebo-controlled trial.
- a. Patients were adults with Group 3 pulmonary hypertension diagnosed by right heart catheterization. The mean age was 66.5 years, 46.9% were female and majority had the diagnosis of idiopathic interstitial pneumonia (in 44.8%).
 - b. Primary efficacy outcome measure of difference between the two groups in the change in peak 6-minute walk distance from baseline to week 16 was met with a difference of 31.12 m (95% confidence interval [CI], 16.85 to 45.39; $P < 0.001$).
 - c. Clinical worsening was evaluated as a secondary endpoint and occurred in 37 patients (22.7%) in the treprostinil group, as compared with 54 patients (33.1%) in the placebo group (hazard ratio, 0.61; 95% CI, 0.40 to 0.92; $P = 0.04$ by the log-rank test)
 - d. There was no significant between-group difference in patient-reported quality of life as assessed with the SGRQ or in the distance–saturation product at week 16
 - e. The most frequently reported adverse events were cough, headache, dyspnea, dizziness, nausea, fatigue, and diarrhea. Serious adverse events occurred in 23.3% of the patients who received inhaled treprostinil and in 25.8% of those who received placebo.
- XXIX. Patients who have shown intolerance or significant lack of efficacy to a prostacyclin or prostacyclin analogue that resulted in discontinuation or inability to effectively titrate that therapy were excluded from the clinical trial. There is a lack of clinical trial data to show that Treprostinil (Tyvaso) would be effective or safe in this patient population.

Investigational Uses

- I. Ambrisentan (generic, Letairis);
 - A. Chronic thromboembolic pulmonary hypertension (CTEPH)
 - a. AMBER I is a phase 3, randomized, double-blind, placebo controlled, parallel group, 16-week study evaluating the safety and efficacy of ambrisentan and placebo in subjects with inoperable CTEPH. AMBER II is an open-label, extension study of the long-term safety, tolerability, and efficacy.

- b. These studies were terminated early due to futility of enrollment. This was due to several factors, including an unexpectedly low screening rate (~20% of expected) and high screening failure rate (approaching 60%, mostly due to concerns regarding inoperability raised by the central adjudication committee).
 - B. Digital ulcers (DU) in systemic sclerosis
 - a. A pilot study was conducted to evaluate the efficacy of ambrisentan in the treatment and prevention of digital ulcers in patients with systemic sclerosis and they found that ambrisentan did not prevent the development of new DU over a 4-week time period after 24 weeks. A placebo-controlled study with more patients will be necessary to conclusively assess the effects of ambrisentan on DUs. There is no robust data to support the use of ambrisentan in DUs.
 - C. Lowering Portal Pressure in Patients with Liver Cirrhosis
 - a. A phase II, single-arm, open-label study to characterise the effect on portal pressure, the effect on renal function and the pharmacokinetic profile of ambrisentan in patients with decompensated cirrhosis is being conducted but no results have been published yet.
 - D. Pulmonary Hypertension Associated with Idiopathic Pulmonary Fibrosis
 - a. A Phase 3, randomized, double-blind, placebo-controlled, multi-center, parallel-group study to evaluate the efficacy and safety of ambrisentan in subjects with idiopathic pulmonary fibrosis and pulmonary hypertension called ARTEMIS-PH was terminated.
 - E. Sarcoidosis
 - a. Ambrisentan was studied for Sarcoidosis Associated Pulmonary Hypertension in a single group assignment, open-label clinical trial and suggested a possible benefit of this drug in selected patients. However, the study was a prospective, open-label, proof of concept trial of ambrisentan that wasn't powered enough to show robust safety and efficacy data to support the use.
 - b. There is limited or no published clinical trial data to support the use of ambrisentan in conditions other than Pulmonary Arterial Hypertension (PAH). The clinical trials that were conducted either had very few patients, data was not published, or the studies were terminated.
- II. Bosentan (Tracleer)
 - A. Chronic obstructive pulmonary disease - Pulmonary hypertension
 - a. In a 12-week randomized trial (N=30) in patients with severe, or very severe, COPD who did not have severe pulmonary hypertension at rest, there was no significant between-group difference in change from baseline in the mean 6-minute walking distance. Additionally, from baseline to week 12, the mean arterial partial pressure of oxygen significantly decreased in the bosentan group compared with placebo. Health-related quality of life scores (Short-Form-36 Health Survey) also significantly worsened in the bosentan group compared with placebo.
 - b. In a small, open-label study (N=32), addition of bosentan to best supportive care (BSC) improved the 6-minute walking distance and WHO functional class compared with patients receiving BSC alone. Bosentan plus BSC did not significantly improve baseline pulmonary volumes (functional vital capacity, forced expired volume in 1 second), cardiac index, arterial blood gases (partial pressure of oxygen and carbon dioxide), or quality of life (St. George questionnaire).
 - c. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline does not recommend use of bosentan for treating patients with severe COPD.
 - B. Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

- a. Bosentan was studied in a prospective, phase III, randomized, placebo-controlled, double-blind, multicenter, parallel group study to assess the efficacy, safety and tolerability in 157 patients with inoperable CTEPH (NCT00313222). The primary outcome was change from baseline to week 16 in 6MWD and change from baseline to week 16 in pulmonary vascular resistance (PVR) at rest. A statistically significant treatment effect (TE) on PVR was demonstrated: -24.1% of baseline (95% confidence interval [CI]: -31.5% to -16.0%; $p < 0.0001$). Mean TE on 6-min walk distance was +2.2 m (95% CI: -22.5 to 26.8 m; $p = 0.5449$) which is not statistically significant.
- b. The BENEFIT open-label, extension study in patients with inoperable CTEPH. In total, 148 of the patients who received randomized treatment rolled over into the extension. The trial data has not been published.
- c. There is limited clinical trial data to support the use of bosentan in CTEPH. The clinical trial showed very limited efficacy and safety data.
- C. Digital ulcers in systemic sclerosis
 - A. In a double-blind, placebo-controlled study, 122 patients with limited or diffuse systemic sclerosis, according to American College of Rheumatology criteria, and documented digital ulcer within the previous 12 months were randomized 2:1 to treatment with oral bosentan (79 patients) or placebo (43 patients). Mean patient age was 51.8 years, and 63% of patients had digital ulcers at baseline. In patients receiving bosentan, the number of new digital ulcers was significantly reduced compared with placebo ($P=0.0083$), averaging 1.4 and 2.7 new ulcers per patient, respectively. Of patients with digital ulcers at baseline, an average of 1.8 new ulcers occurred per bosentan-treated patient and an average of 3.6 new ulcers occurred per placebo-treated patient, a reduction of 50% ($P=0.0075$). There was a slight improvement in Scleroderma Health Assessment Questionnaire (SHAQ) scores that did not reach statistical significance, except for hand function which was significantly improved in bosentan-treated patients. In patients with diffuse scleroderma with digital ulcers at baseline, 11% of bosentan-treated patients developed 4 or more new ulcers and 0% developed 7 or more new ulcers, compared with 50% and 20% of patients in the placebo group. There was no significant difference in time to complete or partial healing of ulcers between groups; however, there was a slight trend toward slower healing in patients treated with bosentan. Adverse effects of bosentan included diarrhea (7 [8.9%] patients) and elevated transaminase levels (9 [11.4%] patients). Five patients in the bosentan group withdrew because of abnormal liver function tests.
- D. Essential hypertension
 - a. There is no evidence that differentiates safety and efficacy of bosentan from other traditional medications (diuretics, CCB, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), and alfa and beta blockers).
- E. Raynaud phenomenon in systemic sclerosis
 - a. Data from controlled and uncontrolled trials evaluating bosentan (Tracleer) in the management of secondary Raynaud phenomenon demonstrate conflicting results in clinical and microvascular assessments. According to evidence-based international consensus-derived recommendations, bosentan has no confirmed efficacy in the treatment of active digital ulcers in systemic sclerosis patients but is effective in the prevention of digital ulcers, particularly multiple ulcers, and should be considered after other therapies have failed.
- F. Thromboembolic pulmonary hypertension, chronic

- a. A systematic review identified 2 randomized trials of 182 patients with chronic thromboembolic pulmonary hypertension that compared 16 weeks of treatment with bosentan (Tracleer) versus placebo. Bosentan (Tracleer) significantly improved the cardiopulmonary hemodynamic parameters of cardiac index and pulmonary vascular resistance. Bosentan (Tracleer) did not significantly affect the 6-minute walk distance, mean pulmonary arterial pressure, risk of functional class deterioration, or risk of clinical worsening. The risk of liver function abnormality was significantly increased with bosentan (Tracleer).
- III. Macitentan (Opsumit);
- A. Chronic thromboembolic pulmonary hypertension (CTEPH)
 - a. The safety, tolerability and efficacy of macitentan in subjects with inoperable chronic thromboembolic pulmonary hypertension were evaluated in MERIT-1 and MERIT-2:
 - i. MERIT-1 is a prospective, randomized, placebo-controlled, double-blind, multicenter, parallel-group, 24-week study to assess the efficacy, safety and tolerability in 80 patients. The primary efficacy endpoint is defined as the pulmonary vascular resistance (PVR) at rest at week 16 expressed as percent of baseline PVR at rest and the geometric mean PVR at rest decreased to 73·0% (95% CI 63·6–83·8) of the baseline value in the macitentan group, corresponding to a mean decrease from baseline of 206 dyn·s/cm⁵, and decreased to 87·2% (95% CI 78·5–96·7) of the baseline value in the placebo group, corresponding to a mean decrease from baseline of 86 dyn·s/cm⁵ (ratio of geometric means 0·84, 95% CI 0·70–0·99, p=0·041). The trial did not include patients from the United States of America, included a small patient population and was short term.
 - ii. MERIT-2 is an ongoing, long-term, multicenter, single-arm, open-label extension study of the MERIT-1 study, to assess safety, tolerability and efficacy. Results from this trial have not been reported at this time.
 - b. There is insufficient clinical trial data to support the use of macitentan in patients with CTEPH. Clinical trials are ongoing to further evaluate macitentan for CTEPH.
 - B. Digital ulcers in systemic sclerosis
 - a. A prospective, randomized, placebo-controlled, double-blind, multicenter, parallel group study to assess the efficacy, safety and tolerability of macitentan in patients with ischemic digital ulcers associated with systemic sclerosis was terminated.
 - b. Two international, randomized, double-blind, placebo-controlled trials (DUAL-1, DUAL-2) were conducted in patients with systemic sclerosis and active digital ulcers at baseline. The primary outcome for each trial was the cumulative number of new digital ulcers from baseline to week 16. The results of the studies do not support the use of macitentan for the treatment of digital ulcers in this patient population.
 - C. Glioblastoma
 - a. A single-center, open-label, phase 1 study of concurrent therapy with macitentan, radiotherapy, and temozolomide, followed by maintenance therapy with macitentan and temozolomide in subjects with newly diagnosed glioblastoma was terminated due to low recruitment.
 - b. A Phase 1/1b, open-label study in patients with recurrent glioblastoma to assess the safety and tolerability of macitentan in combination with dose-dense temozolomide was terminated because the results did not clearly support continuing development in recurrent GBM.

- c. There is limited or no published clinical trial data to support the use of macitentan in conditions other than Pulmonary Arterial Hypertension (PAH). The clinical trials that were conducted had very few patients, no robust data, terminated, or data was not published.
- IV. Riociguat (Adempas);
 - A. Systemic sclerosis-associated digital ulcers
 - a. Seventeen participants (eight placebo, nine riociguat) were randomized at five centers. Baseline characteristics were comparable between the treatment groups, except for participants who were randomized to placebo were older and had longer disease duration. Treatment with riociguat did not reduce the number of DU net burden compared with placebo at 16 weeks. Open-label extension suggests that longer duration is needed to promote DU healing, which needs to be confirmed in a new trial.
 - b. The conducted trials are not powered enough and show low or no efficacy. There is limited to no published clinical trial data to support the use of riociguat (Adempas) in conditions other than persistent/recurrent Chronic Thromboembolic Pulmonary Hypertension (CTEPH) or Pulmonary Arterial Hypertension (PAH).
- IX. Treprostinil (Tyvaso; Tyvaso DPI);
 - A. Pulmonary hypertension (PH) WHO Groups II-V
 - Group II - Left heart disease, including congestive heart failure (CHF)
 - Group III – Non-ILD lung diseases, including chronic obstructive pulmonary disease (COPD), bronchiectasis; Other lung disease with mixed obstruction and restriction (e.g., pulmonary fibrosis with emphysema); Hypoxia without lung disease (e.g., high altitude, sleep-disordered breathing, obesity hypoventilation)
 - Group IV - Chronic thrombotic and/or embolic disease
 - Group V – Sarcoidosis

There is limited or no published clinical trial data to support the use of treprostinil (Tyvaso) in conditions other than PAH and PH due to ILD. The clinical trials that were conducted had very few patients, no robust data, were terminated, or data was not published.
- X. Iloprost (Ventavis), treprostinil (Orenitram) and selexipag (Uptravi);
 - A. Pulmonary hypertension (PH) WHO Groups II-V
 - Group II - Left heart disease, including congestive heart failure (CHF)
 - Group III - Lung diseases, including chronic obstructive pulmonary disease (COPD), bronchiectasis, and idiopathic pulmonary fibrosis (IPF); Other lung disease with mixed obstruction and restriction (e.g., pulmonary fibrosis with emphysema; Hypoxia without lung disease (e.g., high altitude, sleep-disordered breathing, obesity hypoventilation)
 - Group IV - Chronic thrombotic and/or embolic disease
 - Group V – Sarcoidosis
 - B. There is limited or no published clinical trial data to support the use of iloprost (Ventavis), treprostinil (Orenitram) and selexipag (Uptravi) in conditions other than Pulmonary Arterial Hypertension (PAH). The clinical trials that were conducted had very few patients, no robust data, were terminated, or data was not published.
- IV. Iloprost (Ventavis), treprostinil (Tyvaso), treprostinil (Orenitram) and selexipag (Uptravi);
 - A. Chronic thromboembolic pulmonary hypertension (CTEPH) – WHO Group IV
 - a. There is insufficient data to support the use of selexipag (Uptravi) in patients with inoperable or persistent/recurrent after surgical and/or interventional treatment CTEPH. Clinical trial was terminated as the study did not demonstrate efficacy on the primary endpoint, PVR vs. placebo at wk 20 at a planned interim analysis.

- b. There is limited or no published clinical trial data to support the use of iloprost (Ventavis), treprostinil (Tyvaso), treprostinil (Orenitram) and selexipag (Uptravi) in conditions other than Pulmonary Arterial Hypertension (PAH). The clinical trials that were conducted had very few patients, no robust data, were terminated, or data was not published.

Appendix

I. Table 1: PAH Determinants of Prognosis (ACCF/AHA Guidelines)

Determinants of Risk	Lower Risk (Good Prognosis)	Higher Risk (Poor Prognosis)
Clinical evidence of RV failure	No	Yes
Progression of symptoms	Gradual	Rapid
WHO class†	II, III	IV
6MW distance‡	Longer (greater than 400 m)	Shorter (less than 300 m)
CPET	Peak VO ₂ greater than 10.4 mL/kg/min	Peak VO ₂ less than 10.4 mL/kg/min
Echocardiography	Minimal RV dysfunction	Pericardial effusion, significant RV enlargement/dysfunction, right atrial enlargement
Hemodynamics	RAP less than 10 mm Hg, CI greater than 2.5 L/min/m ²	RAP greater than 20 mm Hg, CI less than 2.0 L/min/m ²
BNP§	Minimally elevated	Significantly elevated
*Most data available pertains to IPAH. Little data is available for other forms of PAH. One should not rely on any single factor to make risk predictions.		
†WHO class is the functional classification for PAH and is a modification of the New York Heart Association functional class.		
‡6MW distance is also influenced by age, gender, and height.		
§As there is currently limited data regarding the influence of BNP on prognosis, and many factors including renal function, weight, age, and gender may influence BNP, absolute numbers are not given for this variable.		
6MW indicates 6-minute walk; BNP, brain natriuretic peptide. CI, cardiac index; CPET, cardiopulmonary exercise testing; peak VO ₂ , average peak oxygen uptake during exercise; RAP, right atrial pressure; RV, right ventricle; and WHO, World Health Organization.		

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Policy Implementation/Update:

Action and Summary of Changes	Date
Addition of Yutrepia capsules.	07/2025
Updated supporting evidence section for the requirement of two treatment groups (e.g., ERA, PDE5 inhibitor, or riociguat) before gaining access to prostacyclin derivatives or prostacyclin receptor agonists	06/2025
Added tadalafil/macitentan (Opsumit) in the setting of group 1 PAH; Updated supporting evidence, references.	09/2024
Added sotatercept (Winrevair) in the setting of group 1 PAH; Updated supporting evidence	08/2024
Added Tyvaso DPI product. In the setting of PAH: Updated oral and inhaled prostacyclins (e.g., treprostinil) to require previous trial of two within a PDE-5, ERA, or riociguat. Removed requirement of a PDE-5 prior to approval of an ERA. Updated initial approval duration to be 6 months for all products.	04/2023
- Added new indication of PH due to ILD for treprostinil (Tyvaso) - Added treprostinil injection (Remodulin) into policy - Removed requirement of PDE-5 monotherapy for 3 months in those requesting generic ambrisentan in combination with a PDE-5 - Added requirement of prior endothelin receptor antagonist if requesting Ventavis or Tyvaso in PAH	06/2021
- Updated renewal section with standard renewal language - Added chronic thromboembolic pulmonary hypertension (CTEPH) as an investigational indication to bosentan (generic, Tracleer), ambrisentan (generic, Letairis), macitentan (Opsumit) and selexipag (Uptravi)	03/2020
- Updated the criteria into policy format - Added acute vasoreactivity test criteria to apply to all agents - Added age limit to reflect clinical trial data - Combined criteria for bosentan (generic, Tracleer), ambrisentan (generic, Letairis) & macitentan (Opsumit) with riociguat (Adempas) criteria and iloprost (Ventavis), treprostinil (Tyvaso and Orenitram), selexipag (Uptravi) - Quantity limit change iloprost (Ventavis) and bosentan (Letairis) to reflect the dosing in the package insert - Treprostinil (Orenitram) 5mg doseage form added	12/2019

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- Added criteria because generic bosentan and generic ambrisentan became available we are driving patients to a more cost effective option; - Prior to getting bosentan (Tracleer), member has tried generic bosentan and treatment has been ineffective, contraindicated, or not tolerated - Prior to getting ambrisentan (Letairis), member has tried generic ambrisentan and treatment has been ineffective, contraindicated, or not tolerated - Added generic bosentan and generic ambrisentan to the policy	
- Added Uptravi for P&T 5/4/16 - Reviewed policy	3/29/2016
- Updated formatting. - Added Tyvaso and Orenitram, removed question regarding initial 6 minute walking distance and required trial and failure of generic sildenafil only for oral prostanoid.	03/17/2016
- Criteria update: Validated place in therapy and recommendations. - Removed questions regarding contraindications, warnings/precautions. - Updated header, footer and formatting [riociguat (Adempas)] - Reviewed	03/14/2016
Policy created and effective [iloprost (Ventavis), treprostinil (Tyvaso), treprostinil (Orenitram) and selexipag (Uptravi)]	Prior to 3/17/2016 (no date available)
Policy created [ambrisentan (Letairis), bosentan (Tracleer) and macitentan (Opsumit)]	03/2016
Previously reviewed [ambrisentan (Letairis), bosentan (Tracleer) and macitentan (Opsumit)]	03/2014, 03/2016
Criteria for ambrisentan (Letairis), bosentan (Tracleer) and macitentan (Opsumit) created	01/2013

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP234

Description

Pyrimethamine (Daraprim) is an orally administered antiparasitic agent that reversibly inhibits the protozoal enzyme dihydrofolate reductase, selectively blocking conversion of dihydrofolic acid to its functional form, tetrahydrofolic acid.

Length of Authorization

- I. Initial: Six months
- II. Renewal:
 - i. **Congenital toxoplasmosis:** Six months, maximum one-time renewal
 - ii. **All other indications:** 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit	
			Pediatric	Adult
Pyrimethamine (Daraprim)	25 mg tablets	Toxoplasmosis prophylaxis	30 tablets / 30 days	30 tablets / 30 days
		Toxoplasmosis treatment	30 tablets / 30 days	First month: 98 tablets / 30 days Maintenance: 90 tablets / 30 days
		Congenital toxoplasmosis	First six months: 30 tablets / 30 days Last six months: 10 tablets / 30 days	N/A
		<i>Pneumocystis jiroveci</i> pneumonia prophylaxis	N/A	30 tablets / 30 days
		Cystoisosporiasis (isoporiasis) treatment	30 tablets / 30 days	90 tablets / 30 days

Initial Evaluation

- I. **Generic or compound pyrimethamine (Daraprim)** may be considered medically necessary when the following criteria are met:
 - A. Medication is prescribed by, or in consultation with, an infectious disease specialist; **AND**
 - B. Treatment with pyrimethamine compound formulation (e.g., solution, suspension, capsule) has been ineffective, contraindicated, or not tolerated; **AND**
 - C. A diagnosis of one of the following:

1. **Toxoplasmosis prophylaxis; AND**
 - i. Documentation that the member is in an immunocompromised state (e.g., AIDS/HIV, transplant, cancer, or taking immunosuppressive drugs [e.g., corticosteroids, non-biologic, non-specialty DMARD (e.g., methotrexate, cyclosporine, acitretin, azathioprine, etc.), mycophenolate, biologics (e.g., adalimumab, etanercept), etc.]); **AND**
 - ii. Seropositive for anti-toxoplasma immunoglobulin G (IgG); **AND**
 - iii. Documentation that treatment with trimethoprim- sulfamethoxazole (TMP-SMX) has been ineffective, contraindicated, or not tolerated; **AND**
 - iv. Treatment with pyrimethamine will be used in combination with leucovorin and an antimicrobial agent (e.g., sulfonamide [sulfadiazine, sulfamethoxazole/trimethoprim], dapsone, clindamycin, or atovaquone); **OR**
2. **Toxoplasmosis treatment**
 - i. Seropositive for anti-toxoplasma immunoglobulin G (IgG); **AND**
 - a. Presence of active radiographic changes (one or more contrast-enhancing lesions, edema); **OR**
 - b. Presence of clinical symptoms (e.g., fever, lymphadenopathy, chorioretinitis, headache, or motor weakness); **AND**
 - ii. Treatment with pyrimethamine will be used in combination with leucovorin and an antimicrobial agent (e.g., sulfonamide [sulfadiazine, sulfamethoxazole/trimethoprim], dapsone, clindamycin, or atovaquone); **OR**
3. **Congenital toxoplasmosis; AND**
 - i. Treatment with pyrimethamine will be used in combination with leucovorin and an antimicrobial agent (e.g., sulfonamide [sulfadiazine, sulfamethoxazole/trimethoprim], dapsone, clindamycin, or atovaquone); **OR**
4. ***Pneumocystis jiroveci* pneumonia (PCP) prophylaxis; AND**
 - i. Documentation that the member is in an immunocompromised state (e.g., AIDS/HIV, transplant, cancer, or taking immunosuppressive drugs [e.g., corticosteroids, non-biologic, non-specialty DMARD (e.g., methotrexate, cyclosporine, acitretin, azathioprine, etc.), mycophenolate, biologics (e.g., adalimumab, etanercept), etc.]); **AND;**
 - ii. Treatment with pyrimethamine will be used in combination with leucovorin and an antimicrobial agent (e.g., sulfonamide [sulfadiazine, sulfamethoxazole/trimethoprim], dapsone, clindamycin, or atovaquone); **AND**
 - iii. Treatment with trimethoprim- sulfamethoxazole (TMP-SMX) has been ineffective or contraindicated; **OR**
 - iv. Treatment with trimethoprim- sulfamethoxazole (TMP-SMX) has been not tolerated; **AND**
 - a. Member has been re-challenged with trimethoprim-sulfamethoxazole (TMP-SMX) using a desensitization protocol, or and is still unable to tolerate; **OR**
5. **Cystoisosporiasis treatment; AND**

- i. Treatment with pyrimethamine will be used in combination with leucovorin;
AND
 - ii. Treatment with one of the following has been ineffective, contraindicated, or not tolerated:
 - a. Oral trimethoprim- sulfamethoxazole (TMP-SMX); **OR**
 - b. IV trimethoprim- sulfamethoxazole (TMP-SMX); **OR**
 - c. Ciprofloxacin
- II. **Brand pyrimethamine (Daraprim)** may be considered medically necessary when the following criteria below are met:
 - A. Criteria I(A)-I(C) above are met; **AND**
 - B. In the absence of a drug shortage, coverage of the multi-source brand drug is to be considered medically necessary when the prescriber is requesting the multi-source brand drug due to a documented adverse reaction to the generic equivalent; **AND**
 - C. If the provider has not reported this reaction to MedWatch, please acknowledge the Health Plan or Specialty Pharmacy may report the reaction to MedWatch and may need to contact the provider for more information regarding reaction details for adequate reporting; **AND**
 - D. The prescriber must document one or more of the following, indicating that the reaction:
 - 1. Was life-threatening; **OR**
 - 2. Required hospitalization; **OR**
 - 3. Required intervention to prevent impairment or damage; **OR**
 - E. The prescriber is requesting the brand name drug due to a documented allergy to the generic equivalent [i.e., skin rashes (particularly hives), itching, respiratory complications and angioedema] that required medical intervention to prevent impairment or damage; **OR**
 - F. The prescriber is requesting the brand name drug due to a documented intolerance to the generic equivalent which caused disability, rendering the patient unable to function or perform activities of daily living; **AND**
 - 1. More than one generic equivalent has been tried, or there is only one generic equivalent for the prescribed brand drug.
- III. Pyrimethamine (Daraprim) is considered not medically necessary when criteria above are not met and/or when used for:
 - A. Prevention or treatment of malaria.
- IV. Pyrimethamine (Daraprim) is considered investigational when used for all other conditions.

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**

- III. Member has exhibited improvement or stability of disease symptoms (e.g., CD4 count recovery, contrast-enhancing lesions, improvement in symptoms such as fever, lymphadenopathy, chorioretinitis, or headache); **AND**
- IV. Request is for compound pyrimethamine; **OR**
- V. If request is for generic pyrimethamine:
 - a. Provider attests that the member remains ineligible to transition to compounded pyrimethamine products (e.g., solution, suspension, or capsule); **OR**
- VI. If the request is for Brand Daraprim:
 - a. Provider attests that the member remains ineligible to transition to compounded pyrimethamine products (e.g., solution, suspension, or capsule) or generic pyrimethamine tablets.

Supporting Evidence

- I. Pyrimethamine (Daraprim) is not considered a narrow therapeutic index drug, therefore there are no foreseeable pharmacokinetic or clinical implications in transitioning a patient from an oral generic formulation to a compounded formulation.
- II. There is no universal standard scale for quantifying an immunocompromised state. The National Institute of Health National Cancer Institute defines immunocompromised (also called immunosuppressed) as having a weakened immune system and reduced ability to fight infections and other diseases. This may be caused by certain conditions, such as AIDS, cancer, diabetes, malnutrition, and certain genetic disorders. It may also be caused by certain treatments, such as biologics, corticosteroids, DMARDS, oncolytics, radiation therapy, and stem cell or organ transplant.
- III. Opportunistic infections (OIs) are illnesses that occur more frequently and are more severe in people with compromised immune systems, including HIV, hematopoietic cell transplant, solid organ transplant, cancer-related immunosuppression and hematological malignancies, or taking immunosuppressive therapies. Due to the complexity of opportunistic infections, pyrimethamine needs to be prescribed by, or in consultation with, an infectious disease specialist.
- IV. Initial serological screening should be performed to determine whether the member has ever been infected or is acutely or chronically infected with toxoplasmosis. *Toxoplasma*-specific IgG and IgM tests can be performed at any commercial, non-reference, or hospital-based laboratory. A positive serologic anti-toxoplasma IgG antibody test establishes that the member has been infected and is at risk of reactivation during periods of significant immunosuppression.
- V. Pyrimethamine must be taken in combination with leucovorin and an antimicrobial agent due to enhanced safety and efficacy. Administration with leucovorin is recommended to reduce incidence of hematologic adverse events (myelosuppression) while taking pyrimethamine. Pyrimethamine and an antimicrobial agent act synergistically by inhibiting proliferation and survival through inhibiting the folate metabolic pathway.
- VI. **Toxoplasmosis prophylaxis**
 - a. TMP-SMX should be considered first line therapy for toxoplasmosis prophylaxis. TMP-SMX also provides protection against other pathogens, including PCP, Nocardia, enteric pathogens, Plasmodium species, urinary pathogens, and some respiratory pathogens. The broader spectrum of activity of TMP-SMX is among the reasons this drug is preferred.
 - b. In adults and adolescents with HIV, toxoplasmosis prophylaxis should be discontinued in patients receiving ART whose CD4 counts increase to >200 cells/mm³ for more than 3 months.

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Toxoplasmosis prophylaxis should be discontinued because it adds little value in preventing toxoplasmosis and increases pill burden, potential for drug toxicity and interaction, and likelihood of development of drug-resistant pathogens.

- c. There is no consensus concerning initiation and duration of toxoplasmosis prophylaxis in immunocompromised members. Regarding the incidence rate of toxoplasmosis following hematopoietic stem cell transplant (HSCT) and solid organ transplant (SOT), prophylaxis should be maintained for at least 6 months post-transplant. It should be prolonged in cases of graft-versus-host disease, prolonged neutropenia, and prolonged administration of corticosteroids.
- d. In immunocompetent individuals, acute toxoplasmosis infection is usually self-limited and rarely symptomatic, although cases of severe infection due to rare *Toxoplasma* genotypes have been reported. Treatment for toxoplasmosis is not required for immunocompetent members who are asymptomatic or have mild, uncomplicated acute toxoplasmosis.

VII. **Toxoplasmosis treatment**

- a. Toxoplasmosis therapy requires serologic anti-toxoplasma IgG detection, radiographic changes (CT or MRI with multiple contrast-enhancing lesions in the grey matter of the cortex or basal ganglia, often with associated edema), and/or presence of clinical symptoms. Common clinical manifestations include lymphadenopathy, chorioretinitis (a type of posterior uveitis), headache, confusion, and motor weakness. The radiologic goals for treatment include resolution of the lesion(s) in terms of size, contrast enhancement, and associated edema, although residual contrast-enhancing lesions may persist for prolonged periods
- b. In members with HIV, acute therapy for toxoplasmosis must be continued for at least 6 weeks. Longer courses may be necessary if clinical or radiologic disease is extensive, or response is incomplete at 6 weeks. After completion of the acute therapy, guidelines recommend members who have completed a 6-week treatment course for acute toxoplasmosis therapy should be given chronic maintenance therapy to suppress infection until immune reconstitution occurs as a consequence of antiretroviral therapy (ART). Members receiving chronic maintenance therapy for toxoplasmosis are at low risk for recurrence if they have successfully completed initial therapy, remain asymptomatic regarding signs and symptoms of toxoplasmosis, and have an increase in their CD4 counts to >200 cells/mm³ after ART that is sustained for more than 6 months.

VIII. **Congenital toxoplasmosis**

- a. Pregnant women with suspected or confirmed primary toxoplasmosis and newborns with possible or documented congenital toxoplasmosis should be managed in consultation with an appropriate infectious disease specialist. Empiric therapy should be strongly considered for newborns of HIV-infected mothers who had symptomatic or asymptomatic primary *Toxoplasma* infection during pregnancy, regardless of whether treatment was administered during pregnancy. The recommended duration of treatment for congenital toxoplasmosis in infants is 12 months (continuously throughout the first year of life).

IX. ***Pneumocystis jiroveci* pneumonia (PCP) prophylaxis**

- a. The preferred PCP prophylaxis regimen for HIV and immunocompromised non-HIV infected patients is TMP-SMX, because of its superior efficacy compared with aerosolized pentamidine, oral dapsone, or oral atovaquone. TMP-SMX chemoprophylaxis should be continued, when clinically feasible, in patients who have non-life-threatening adverse reactions. In those who discontinue TMP-SMX because of a mild adverse reaction, re-

institution of the drug should be considered after the reaction has resolved. Oral desensitization regimens have been used successfully for HIV-infected patients with fever and rash, and similar protocols have been used in HCT recipients with a success rate of approximately 80%. Therapy should be permanently discontinued (with no rechallenge) in patients with life-threatening adverse reactions including possible or definite Stevens-Johnson syndrome or toxic epidermal necrolysis.

- b. PCP prophylaxis should be discontinued in adult and adolescent members who have responded to ART with an increase in CD4 counts from 200 cells/mm³ for >3 months. Discontinuation of primary PCP prophylaxis in patients with CD4 count increase to >200 cells/mm³ as a result of ART is recommended because its preventive benefits against PCP, toxoplasmosis, and bacterial infections are limited; stopping the drugs reduces pill burden, cost, and the potential for drug toxicity, drug interactions, and selection of drug-resistant pathogens.
- c. PCP prophylaxis and treatment with pyrimethamine is not indicated for pediatric members. TMP-SMX is a first line prophylaxis agent due to its high efficacy, relative safety, low cost, and broad antimicrobial spectrum. Dapsone or atovaquone are second line effective and safe prophylaxis regimens available for pediatric patients unable to take TMP-SMX.

X. Cystoisosporiasis treatment

- a. Cystoisosporiasis (also known as isosporiasis) should not be confused with Cryptosporidiosis. Cystoisosporiasis has also been reported immunocompromised as well as in immunocompetent individuals. In adults and adolescents with HIV, chemoprophylaxis with oral trimethoprim-sulfamethoxazole (TMP-SMX) has been associated with a lower incidence or prevalence of isosporiasis. Intravenous administration of TMP-SMX should be considered for patients with potential or documented malabsorption. Ciprofloxacin is considered a second-line alternative.
- b. In a randomized, placebo-controlled trial, daily TMP-SMX (160/800 mg) was protective against isosporiasis in persons with early-stage HIV infection (World Health Organization clinical stage 2 or 3 at enrollment). In an observational study, incidence of isosporiasis decreased after widespread introduction of antiretroviral therapy (ART), except in patients with CD4 counts <50 cells/mm³. After adjustment for the CD4 T lymphocyte (CD4) cell count, the risk of isosporiasis was substantially lower in those receiving prophylaxis with TMP-SMX, sulfadiazine, or pyrimethamine.

XI. In the United States, the Office of Generic Drugs at the Food and Drug Administration (FDA) follows a rigorous review process to make sure that, compared to the brand name (or innovator) medications, the proposed generic medications:

- a. Contain the same active/key ingredient
- b. Have the same strength
- c. Use the same dosage form (for instance, a table, capsule, or liquid) and
- d. Use the same route of administration (for instance, oral, topical, or injectable)

XII. The FDA's review process also ensures that generic medications perform the same way in the human body and have the same intended use as the name brand medication. Healthcare professionals and consumers can be assured that FDA-approved generic drug products have met the same rigid manufacturing standards as the innovator drug. In addition, FDA inspects facilities to

make certain the generic manufacturing, packaging, and testing sites pass the same quality standards as those of brand-name drugs.

- a. Thus, when an adverse reaction or allergy occurs to any medication (brand or generic), it is important to report to MedWatch.
- b. In order to keep effective medical products available on the market, the FDA relies on the voluntary reporting of these events. This information is used to maintain safety surveillance and to monitor if modifications in use or design of the product are warranted to increase patient safety.

XIII. It can be difficult to distinguish an allergy from a distinct adverse event related to the generic, therefore any event thought to be related to the medication should be reported to MedWatch.

- a. As defined by the American Academy of Allergy, Asthma, and Immunology, an allergic reaction occurs when the immune system overreacts to a substance, triggering an allergic reaction. Sensitivities to drugs may produce similar symptoms, but do not involve the immune system. Only 5-20% of adverse reactions to drugs are considered true allergic reactions. The chances of developing an allergy are higher when you take the medication frequently or when it is rubbed on the skin or given by injection, rather than taken by mouth. The most frequent types of allergic symptoms to medications include skin rashes (particularly hives), itching, respiratory complications and angioedema. The most severe form of immediate allergic reactions is anaphylaxis, and symptoms include hives, facial or throat swelling, wheezing, light-headedness, vomiting and shock.

Investigational or Not Medically Necessary Uses

- I. The use of pyrimethamine for prophylaxis or treatment of malaria in adults is no longer recommended in the CDC Guidelines for the Treatment of Malaria in the United States.

Appendix

Please note, specific doses vary among non-HIV conditions. Dosing regimens listed below are not all inclusive. Please cross-reference compendia for member-specific dose.

- I. Table 1: Recommendations for Preventing and Treating Toxoplasmosis in Adults and Adolescents with HIV²

Indication	Preferred regimen	Alternative regimens	Treatment duration
Toxoplasmosis Prophylaxis	TMP-SMX 1 DS PO daily	• TMP-SMX 1 DS PO three times weekly, or • TMP-SMX SS PO daily, or • Dapsone 50 mg PO daily + (pyrimethamine 50 mg + leucovorin 25 mg) PO weekly, or • (Dapsone 200 mg + pyrimethamine 75 mg + leucovorin 25 mg) PO weekly, or • Atovaquone 1500 mg PO daily, or • (Atovaquone 1500 mg + pyrimethamine 25 mg + leucovorin 10 mg) PO daily	• CD4 count >200 cells/ mm³ for >3 months in response to ART; or • Can consider if CD4 count is 100-200 cells/ mm³ and HIV RNA levels remain below limits of detection for at least 3-6 months
			Indication for Restarting Primary Prophylaxis: • CD4 count < 100 – 200 cells/ mm³

Treating acute Toxoplasmosis*	Induction: Pyrimethamine 200 mg PO once , followed by dose based on body weight: Body weight ≤60 kg: - pyrimethamine 50 mg PO daily + sulfadiazine 1000 mg PO q6h + leucovorin 10–25 mg PO daily (can increase to 50 mg daily or BID) Body weight >60 kg: - pyrimethamine 75 mg PO daily + sulfadiazine 1500 mg PO q6h + leucovorin 10–25 mg PO daily (can increase to 50 mg daily or BID)	Preferred alternative for patients intolerant of sulfadiazine or who do not respond to pyrimethamine-sulfadiazine: - Pyrimethamine (leucovorin)[†] plus clindamycin 600 mg IV or PO q6h + must add additional agent for PCP prophylaxis, or - TMP-SMX (TMP 5 mg/kg and SMX 25 mg/kg) (IV or PO) BID, or - Atovaquone 1500 mg PO BID + pyrimethamine (leucovorin)[†], or - Atovaquone 1500 mg PO BID + sulfadiazine, or - Atovaquone 1500 mg PO BID	- At least 6 weeks; longer duration if clinical or radiologic disease is extensive or response is incomplete at 6 weeks - After completion of the acute therapy, all patients should be continued on chronic maintenance therapy
Toxoplasmosis Chronic Maintenance Therapy	Pyrimethamine 25–50 mg PO daily + sulfadiazine 2000–4000 mg PO daily (in 2 to 4 divided doses) + leucovorin 10–25 mg PO daily	- Clindamycin 600 mg PO q8h + (pyrimethamine 25–50 mg + leucovorin 10–25 mg) PO daily; or - TMP-SMX DS 1 tablet BID, or - TMP-SMX DS 1 tablet daily, or - Atovaquone 750–1500 mg PO BID + (pyrimethamine 25 mg + leucovorin 10 mg) PO daily, or - Atovaquone 750–1500 mg PO BID + sulfadiazine 2000–4000 mg PO daily (in 2 to 4 divided doses), or - Atovaquone 750–1500 mg PO BID	- Successfully completed initial therapy, remain asymptomatic of signs and symptoms of toxoplasmosis, and CD4 count >200 cells/mm³ for >6 months in response to ART Criteria for Restarting Secondary Prophylaxis/Chronic Maintenance - CD4 count <200 cells/mm³

* Acute toxoplasma treatment: if pyrimethamine is unavailable or there is a delay in obtaining it, TMP-SMX should be used in place of pyrimethamine-sulfadiazine. For patients with a history of sulfa allergy, sulfa desensitization should be attempted using one of several published strategies. Atovaquone should be administered until therapeutic doses of TMP-SMX are achieved.

[†] Pyrimethamine and leucovorin doses: Same as doses listed in Preferred Regimen for treating acute toxoplasmosis

Acronyms: ART = antiretroviral therapy; BID = twice daily; CD4 = CD4 T lymphocyte cell; DS = double strength; IV = intravenous; PCP = *Pneumocystis* Pneumonia; PO = orally; q(n)h = every “n” hour; SS = single strength; TMP-SMX = trimethoprim-sulfamethoxazole

II. Table 2. Dosing Recommendations for the Prevention and Treatment of Toxoplasmosis in HIV-Exposed and HIV-Infected Children³

Indication	Preferred regimen	Alternative regimens	Treatment Duration / Comments
Primary Prophylaxis	TMP-SMX 150/750 mg/m ² body surface area once daily by mouth	For Children Aged ≥1 Month: - Dapsone 2 mg/kg body weight or 15 mg/ m² body surface area (maximum 25 mg) by mouth once daily, plus - Pyrimethamine 1 mg/kg body weight (maximum 25 mg) by mouth once daily, plus - Leucovorin 5 mg by mouth every 3 days For Children Aged 1–3 Months and >24 Months: - Atovaquone 30 mg/kg body weight by mouth once daily Children Aged 4–24 Months: - Atovaquone 45 mg/kg body weight by mouth once daily, with or without pyrimethamine 1 mg/kg body weight or 15 mg/m² body surface area (maximum 25 mg) by mouth once daily, plus - Leucovorin 5 mg by mouth every 3 days Acceptable Alternative Dosage Schedules for TMP-SMX: - TMP-SMX 150/750 mg/ m² body surface area per dose once daily by mouth 3 times weekly on 3 consecutive days per week - TMP-SMX 75/375 mg/ m² body surface area per dose twice daily by mouth every day - TMP-SMX 75/375 mg/m² body surface area per dose twice daily by mouth TIW on alternate days	Primary Prophylaxis Indicated for: <i>IgG Antibody to Toxoplasma and Severe Immunosuppression:</i> - HIV-infected children aged <6 years with CD4 percentage <15%; HIV infected children aged ≥6 years with CD4 count <100 cells/mm³ Criteria for Discontinuing Primary Prophylaxis: Note: Do not discontinue in children aged <1 year - After ≥6 months of cART, and - Aged 1 to <6 years; CD4 percentage is ≥15% for >3 consecutive months - Aged ≥6 years; CD4 count >200 cells/mm³ for >3 consecutive months Criteria for Restarting Primary Prophylaxis: - Aged 1 to <6 years with CD4 percentage <15% - Aged ≥6 years with CD4 count <100 to 200 cells/mm³
Secondary Prophylaxis (Suppressive Therapy)	- Sulfadiazine 42.5–60 mg/ kg body weight per dose twice daily* (maximum 2–4 g per day) by mouth, plus - Pyrimethamine 1 mg/kg body weight or 15 mg/ m² body surface area (maximum 25 mg) by mouth once daily, plus - Leucovorin 5 mg by mouth once every 3 days	- Clindamycin 7–10 mg/kg body weight per dose by mouth 3 times daily, plus - Pyrimethamine 1 mg/kg body weight or 15 mg/ m² body surface area (maximum 25 mg) by mouth once daily, plus - Leucovorin 5 mg by mouth once every 3 days Children Aged 1–3 Months and >24 Months: - Atovaquone 30 mg/kg body weight by mouth once daily - Leucovorin, 5 mg by mouth every 3 days - TMP-SMX, 150/750 mg/ m² body surface area once daily by mouth Children Aged 4–24 Months: - Atovaquone 45 mg/kg body weight by mouth once daily, with or without pyrimethamine 1 mg/kg body weight or 15 mg/ m² body surface area (maximum 25 mg) by mouth once daily, plus - Leucovorin, 5 mg by mouth every 3 days - TMP-SMX, 150/750 mg/ m² body surface area once daily by mouth	Secondary Prophylaxis Indicated: - Prior toxoplasmic encephalitis Note: Alternate regimens with very limited data in children. TMP-SMX only to be used if patient intolerant to other regimens Criteria for Discontinuing Secondary Prophylaxis If All of the Following Criteria are Fulfilled: - Completed ≥6 months of cART, completed initial therapy for TE, asymptomatic for TE, and - Aged 1 to < 6 years; CD4 percentage ≥15% for >6 consecutive months - Aged ≥6 years; CD4 cell count >200 cells/mm³ for >6 consecutive months Criteria For Restarting Secondary Prophylaxis: - Aged 1 to <6 years with CD4 percentage <15% - Aged ≥6 years with CD4 cell count <200 cells/mm³
Treatment	Congenital Toxoplasmosis: Pyrimethamine loading dose—2 mg/kg body weight	For Sulfonamide-Intolerant Patients: Clindamycin 5–7.5 mg/kg body weight (maximum 600 mg/dose) by mouth or IV per dose given 4 times a	Treatment Duration: 12 months

	by mouth once daily for 2 days, then 1 mg/kg body weight by mouth once daily for 2–6 months, then 1 mg/kg body weight by mouth 3 times weekly, plus • Leucovorin (folinic acid) 10 mg by mouth or IM with each dose of pyrimethamine, plus • Sulfadiazine 50 mg/kg body weight by mouth twice daily Acquired Toxoplasmosis Acute Induction Therapy (Followed by Chronic Suppressive Therapy): • Pyrimethamine: loading dose—2 mg/kg body weight (maximum 50 mg) by mouth once daily for 3 days, then 1 mg/kg body weight (maximum 25 mg) by mouth once daily, plus • Sulfadiazine 25–50 mg/kg body weight (maximum 1–1.5 g/dose) by mouth per dose 4 times daily, plus • Leucovorin 10–25 mg by mouth once daily, followed by chronic suppressive therapy Treatment Duration (Followed by Chronic Suppressive Therapy): • ≥6 weeks (longer duration if clinical or radiologic disease is extensive or response is incomplete at 6 weeks)	day can be substituted for sulfadiazine combined with pyrimethamine and leucovorin	<u>Congenital Toxoplasmosis:</u> • For infants born to mothers with symptomatic Toxoplasma infection during pregnancy, empiric therapy of the newborn should be strongly considered irrespective of the mother’s treatment during pregnancy. <u>Acquired Toxoplasmosis:</u> • Pyrimethamine use requires CBC monitoring at least weekly while on daily dosing and at least monthly while on less than daily dosing. • TMP-SMX—TMP 5 mg/kg body weight plus SMX 25 mg/kg body weight per dose IV or by mouth given twice daily has been used as an alternative to pyrimethamine-sulfadiazine in adults but has not been studied in children. • Atovaquone (for adults, 1.5 g by mouth twice daily—double the prophylaxis dose) in regimens combined with pyrimethamine/leucovorin, with sulfadiazine alone, or as a single agent in patients intolerant to both pyrimethamine and sulfadiazine, has been used in adults, but these regimens have not been studied in children. • Azithromycin (for adults, 900–1,200 mg/day, corresponding to 20 mg/kg/day in children) has also been used in adults combined with pyrimethamine-sulfadiazine, but has not been studied in children. • Corticosteroids (e.g., prednisone, dexamethasone) have been used in children with CNS disease when CSF protein is very elevated (>1,000 mg/dL) or there are focal lesions with significant mass effects, with discontinuation as soon as clinically feasible. • Anticonvulsants should be administered to patients with a history of seizures and continued through the acute treatment; but should not be used prophylactically.
*Note: Sulfadiazine may be given as 2–4 equal doses per day as long as the total daily dose is 85–120 mg/kg body weight. Key to Acronyms: cART = combination antiretroviral therapy; CBC = complete blood count; CD4 = CD4 T lymphocyte; CNS = central nervous system; CSF = cerebrospinal fluid; IgG = Immunoglobulin G; IM = intramuscular; IV = intravenous; TE = toxoplasmic encephalitis; TMP-SMX = trimethoprim-sulfamethoxazole			

III. Table 3. Recommendations for prevention (prophylaxis) of *Pneumocystis jiroveci* pneumonia in adults and adolescents with HIV²

Indication	Preferred regimen	Alternative regimens	Treatment duration
Preventing First Episode of PCP (Primary Prophylaxis)	• TMP-SMX 1 DS tablet PO daily, or • TMP-SMX 1 SS tablet daily	• TMP-SMX 1 DS PO three times weekly, or • Dapsone 100 mg PO daily or 50 mg PO BID, or • Dapsone 50 mg PO daily with (pyrimethamine 50 mg plus leucovorin 25 mg) PO weekly, or • (Dapsone 200 mg plus pyrimethamine 75 mg plus leucovorin 25 mg) PO weekly; or • Aerosolized pentamidine 300 mg via Respigard II™ nebulizer every month, or • Atovaquone 1500 mg PO daily, or • (Atovaquone 1500 mg plus pyrimethamine 25 mg plus leucovorin 10mg) PO daily	• CD4 count increased from <200 cells/ mm³ to ≥200 cells/mm³ for ≥3 months in response to ART • Can consider when CD4 count is 100–200 cells/ mm³ and HIV RNA remains below limit of detection of the assay used for ≥3 months to 6 months Indication for Restarting Primary Prophylaxis: • CD4 count <100 cells/ mm³ regardless of HIV RNA • CD4 count 100–200 cells/mm³ and HIV RNA above detection limit of the assay used
Preventing Subsequent Episode of PCP (Secondary Prophylaxis)	• TMP-SMX 1 DS tablet PO daily, or • TMP-SMX 1 SS tablet daily	• TMP-SMX 1 DS tablet PO three times weekly, or • Dapsone 100 mg PO daily, or • Dapsone 50 mg PO twice daily, or • Dapsone 50 mg PO daily with (pyrimethamine 50 mg plus leucovorin 25 mg) PO weekly, or • (Dapsone 200 mg plus pyrimethamine 75 mg plus leucovorin 25 mg) PO weekly, or • Aerosolized pentamidine 300 mg via Respigard II™ nebulizer every month, or • Atovaquone 1500 mg PO daily with food, or • (Atovaquone 1500 mg plus pyrimethamine 25 mg plus leucovorin 10 mg) PO daily	• CD4 count increased from 200 cells/ mm³ for >3 months as a result of ART, or • Can consider if CD4 count is 100–200 cells/ mm³ and HIV RNA remains below limits of detection of assay used for ≥3 months to 6 months • For patients in whom PCP occurs at a CD4 count >200 cells/ mm³ while not on ART, discontinuation of prophylaxis can be considered once HIV RNA levels are suppressed to below limits of detection of the assay used for ≥3 months to 6 months, although there are no data to support recommendations in this setting. Note: If an episode of PCP occurs at a CD4 count >200 cells/ mm³ while a patient is on ART, it would be prudent to continue PCP prophylaxis for life, regardless of how high the CD4 cell count rises as a consequence of ART. Indications for Restarting Secondary Prophylaxis: • CD4 count <100 cells/ mm³ regardless of HIV RNA • CD4 count 100–200 cells/ mm³ and HIV RNA above detection limit of the assay used
Note: Patients who are receiving pyrimethamine/sulfadiazine for treatment or suppression of toxoplasmosis do not require additional PCP prophylaxis Key to acronyms = ART = antiretroviral therapy; CD4 = CD4 T lymphocyte cell; DS = double strength; IV = intravenously; PCP = Pneumocystis pneumonia; PO = orally; SS = single strength; TMP = trimethoprim; TMP-SMX = trimethoprim-sulfamethoxazole			

IV. Table 4. Dose recommendations for the prevention and treatment of cystoisoporiasis in adults and adolescents with HIV²

Indication	Preferred regimen	Alternative regimens	Treatment duration
Acute cystoisoporiasis therapy infection	• TMP-SMX (160 mg/800 mg) PO (or IV) QID for 10 days, or • TMP-SMX (160 mg/800 mg) PO (or IV) BID for 7–10 days • One approach is to start with TMP-SMX (160 mg/800 mg) BID regimen first, and increase daily dose and/or duration (up to 3–4 weeks) if symptoms worsen or persist • IV therapy for patients with potential or documented malabsorption	For Patients with Sulfa Intolerance: • Pyrimethamine 50–75 mg PO daily + leucovorin 10–25 mg PO daily, or • Ciprofloxacin 500 mg PO BID for 7 days	7- 10 days
Chronic Maintenance Therapy (Secondary Prophylaxis)	In Patients with CD4 Count <200/mm ³ : • TMP-SMX (160 mg/800 mg) PO 3 times weekly	• TMP-SMX (160 mg/800 mg) PO daily, or • TMP-SMX (320 mg/1600 mg) PO 3 times weekly, or • Pyrimethamine 25 mg PO daily + leucovorin 5–10 mg PO daily, or • Ciprofloxacin 500 mg PO 3 times weekly as a second line alternative	Sustained increase in CD4 count >200 cells/mm ³ for >6 months in response to ART and without evidence of active infection
Key to Acronyms: ART = antiretroviral therapy; BID = twice daily; IV = intravenous; PO = orally; QID = four times a day; TMP-SMX = trimethoprim-sulfamethoxazole			

V. Table 5. Dose recommendations for the prevention and treatment of cystoisoporiasis in HIV-Exposed and HIV-Infected Children³

Indication	Preferred regimen	Alternative regimens	Treatment duration / Comments
Primary prophylaxis	There are no U.S. recommendations for primary prophylaxis of isosporiasis.		
Secondary prophylaxis	If Severe Immunosuppression: • Administer TMP-SMX 2.5 mg/kg body weight of TMP component twice daily by mouth 3 times per week	Pyrimethamine 1 mg/kg body weight (maximum 25 mg) plus folinic acid, 10–25 mg by mouth once daily. Second-Line Alternative: • Ciprofloxacin, 10–20 mg/kg body weight given twice daily by mouth 3 times per week	Consider discontinuing secondary prophylaxis in a patient receiving cART after sustained improvement from severe immunosuppression (from CDC immunologic category 3 to CD4 values that fall within category 1 or 2) for longer than 6 months. In adults, the dose of pyrimethamine for secondary prophylaxis (25 mg daily) is lower than the dose for treatment (50–75 mg daily), but no similar data exist for children. Thus, the recommended dosing for secondary prophylaxis in children is 1 mg/kg per dose (maximum 25 mg) once daily. Ciprofloxacin is generally not a drug of first choice in children due to increased incidence of adverse events, including events related to joints and/or surrounding tissues.

Treatment	TMP-SMX 5 mg/kg body weight of TMP component given twice daily by mouth for 10 days	Pyrimethamine 1 mg/kg body weight plus folinic acid 10-25 mg by mouth once daily for 14 days Second-Line Alternatives: • Ciprofloxacin 10–20 mg/kg body weight/day twice daily by mouth for 7 days • Nitazoxanide for 3 consecutive days	If symptoms worsen or persist, the TMP/SMX dose may be increased to 5 mg/kg/day given 3–4 times daily by mouth for 10 days or the duration of treatment may be lengthened. Duration of treatment with pyrimethamine has not been well established. Ciprofloxacin is generally not a drug of first choice in children due to increased incidence of adverse events, including events related to joints and/or surrounding tissues.
Key to Acronyms: CD4 = CD4 T lymphocyte; CDC = Centers for Disease Control and Prevention; cART = combination antiretroviral therapy; TMP-SMX = trimethoprim-sulfamethoxazole			

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Policy Implementation/Update:

Action and Summary of Changes	Date
Updated criteria to policy format; Added initial and renewal length of authorization; Added toxoplasmosis prophylaxis, toxoplasmosis treatment, congenital toxoplasmosis, <i>Pneumocystis jiroveci</i> pneumonia prophylaxis, and cystoisoporiasis treatment intervention criteria for compound, generic, and brand product; Added brand Daraprim requirement; Added supporting evidence and dosing appendix.	06/2021
Policy created	02/2016

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP284

Split Fill Management*

Description

Quizartinib (Vanflyta) is an orally administered selective type II FLT3 inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
quizartinib (Vanflyta)	Acute myeloid leukemia, newly diagnosed, FLT3 mutation-positive, in combination with 7+3 induction and cytarabine consolidation	17.7 mg tablets	60 tablets/30 days
		26.5 mg tablets	60 tablets/30 days

Initial Evaluation

- I. **Quizartinib (Vanflyta)** may be considered medically necessary when the following criteria are met:
 - A. Member is 18 years of age or older; **AND**
 - B. Medication is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
 - C. A diagnosis of **Newly diagnosed acute myeloid leukemia (AML)** when the following are met:
 1. The member has FLT3-ITD mutation-positive AML; **AND**
 2. Medication will not be used in combination with any other oncolytic medication with the exception of the therapies outlined below:
 - i. Standard 7+3 induction (cytarabine and daunorubicin/idarubicin)
 - ii. Cytarabine consolidation therapy; **AND**
 3. The member has received no prior therapy for AML
- II. Quizartinib (Vanflyta) is considered investigational when used for all other conditions, including but not limited to:
 - A. Acute myeloid leukemia in the absence of FLT3 mutation
 - B. Quizartinib (Vanflyta) in combination with oncolytic therapies other than induction and consolidation chemotherapies
 - C. Relapsed/ refractory acute myeloid leukemia (R/R AML)
 - D. Myelodysplastic syndrome (MDS)

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **OR**
 - Member has been established on induction therapy via an inpatient setting; **AND**
 - i. Provider attests that the member initiated quizartinib (Vanflyta) as part of standard 7+3 induction therapy (cytarabine and daunorubicin/idarubicin) for AML; **AND**
 - ii. Quizartinib (Vanflyta) will be used in combination with cytarabine consolidation therapy; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Member has exhibited improvement or stability of disease symptoms [e.g., achieved complete remission (CR)].

Supporting Evidence

- I. Quizartinib (Vanflyta) is a selective type II FLT3 inhibitor studied in combination with chemotherapy as a once daily oral tablet for the treatment of *FLT3*-ITD-positive acute myeloid leukemia (AML). The efficacy and safety of quizartinib (Vanflyta) has not been established in pediatric patients.
- II. An estimated 25% of newly diagnosed AML cases have *FLT3*-ITD mutations which are associated with a higher rate of relapse and poorer clinical outcomes as compared to wild type *FLT3* and *FLT*-TKD mutations. However, long-term impact of *FLT3*-ITD mutations on AML prognosis remains unclear. Given the complexities related to diagnosis treatment and management of AML, treatment in this disease space must be initiated by or in consultation with a specialist, such as an oncologist or hematologist.
- III. Intensive induction therapy [e.g., cytarabine and an anthracycline (7+3) in combination with midostaurin (Rydapt)] followed by post-remission consolidation therapy [high dose cytarabine (HiDAC) + midostaurin (Rydapt)] and/or allogeneic HCT (allo-HCT) in eligible patients has been the standard of care in FLT3-mutated AML. Post induction and consolidation, NCCN recommends maintenance therapy with an FLT3 inhibitor.
- IV. Quizartinib (Vanflyta) was studied in a randomized, multi-center, double-blind, placebo-controlled, phase 3 trial of 539 patients with newly diagnosed FLT3-ITD mutated AML (QuANTUM-First). Trial participants (N=539) aged 20 to 75 were randomized 1:1 to receive either a standard 7 + 3 induction therapy with quizartinib (Vanflyta) or placebo, followed by consolidation with HiDAC plus quizartinib (Vanflyta) or placebo, and/or allo-HCT. This was then followed by maintenance with single agent quizartinib (Vanflyta) or placebo.
- V. The efficacy of quizartinib (Vanflyta) was assessed via overall survival and event free survival (EFS) endpoints. Overall survival in the ITT population was longer with quizartinib (Vanflyta) than placebo (31.9 months, 95% CI 21.0 – NE vs 15.1 months, 13.2 – 26.2; HR 0.774, 0.614 – 0.975; p=0.032). In the population censored for allo-HCT OS also favored quizartinib (Vanflyta) (20.8 months, 95% CI 14.3 – 28.9 vs 12.9 months, 9.2 – 14.7; HR 0.752, 0.75, 0.56–1.01; p=0.055). The key secondary endpoint of EFS per the FDA's definition was not statistically significant (p= 0.24). However, per original protocol with a 56-day cutoff the results did gain statistical significance. In

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the induction treatment failure (ITF) population not achieving CRc remission by the end of induction up to day 56 quizartinib (Vanflyta) was found to be 11.9 months (8.1 – 16.5) as compared to 5.7 months (0.3 – 3.42) in the placebo group (HR 0.72, 95% CI 0.592 – 0.897; pnominal=0.0031). Median duration of complete remission was longer with quizartinib (Vanflyta) than with placebo (38.6 months, 95% CI 21.9–NE vs 12.4 months, 8.8–22.7; HR 0.62, 0.45–0.86) and in patients with complete remission during induction, relapse-free survival was longer with quizartinib (Vanflyta) compared to placebo (39.3 months, 95% CI 22.6–NE vs 13.6 months, 9.7–23.7; HR 0.61, 0.44–0.85).

- VI. The quality of evidence is considered moderate. The clinical trial program for quizartinib (Vanflyta) consisted of a well-designed randomized clinical trial reporting positive results in overall survival, median duration of complete remission, and median relapse-free survival compared to intensive induction and consolidation therapies alone. However, protocol changes that shifted the definition of EFS may impact the FDA’s review of quizartinib (Vanflyta). The effect of allo-HCT on OS and role of long-term quizartinib (Vanflyta) maintenance therapy after chemotherapy has yet to be fully reported. It is unknown how quizartinib (Vanflyta) will compare with other FDA approved medications in the newly diagnosed FLT3-mutated AML population.
- VII. All trial participants experienced mild to moderate adverse events (AE) with similar AE profile between arms as both groups received 7 + 3 induction and HiDAC consolidation therapies. The most common AEs reported for quizartinib (Vanflyta) vs placebo included febrile neutropenia (44% vs 42%), pyrexia (42% vs 41%), diarrhea (37% vs 35%), hypokalemia (35% vs 36%), and nausea (34% vs 31%). Distinguishable side effects included QTc prolongation in 14% of the quizartinib (Vanflyta) patients vs 4% in the placebo group.
- VIII. Quizartinib (Vanflyta) treatment led to a 34% dose interruption rate in clinical trials and a 19% dose reduction rate due to intolerable AEs. Dose reductions due to QTc prolongation were seen in 4% of quizartinib (Vanflyta) patients. Adverse events associated with a fatal outcome occurred in 30 participants (11%) in the quizartinib (Vanflyta) group and 26 (10%) in the placebo group, infections being the most common cause. Two patients (0.8%) treated with quizartinib (Vanflyta) had a cardiac arrest, with recorded ventricular fibrillation in the setting of severe hypokalemia.
- IX. The use of quizartinib (Vanflyta) has not been studied in combination with medications other than 7 + 3 induction and consolidation chemotherapies. Due to lack of safety and efficacy data with a combination regimen, these agents should not be used together.

Investigational or Not Medically Necessary Uses

- I. Quizartinib (Vanflyta) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Acute myeloid leukemia in the absence of FLT3 mutation
 - B. Quizartinib (Vanflyta) in combination with oncolytic therapies other than induction and consolidation chemotherapies
 - C. Relapsed/ refractory acute myeloid leukemia (R/R AML)
 - D. Myelodysplastic syndrome (MDS)

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified*

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medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
midostaurin (Rydapt®)	Acute myeloid leukemia, newly diagnosed, FLT3 mutation-positive, in combination with cytarabine/daunorubicin induction and cytarabine consolidation
Multi-Targeted Tyrosine Kinase Inhibitors (Multi-TKI)	Unresectable Liver Carcinoma
	Advanced Renal Cell Carcinoma
	Locally Recurrent or Metastatic Progressive Thyroid Cancer
	Advanced Soft Tissue Sarcoma
	Recurrent, High-risk or Metastatic Endometrial Carcinoma
gilteritinib (XOSPATA®)	Relapse/Refractory FLT3 AML

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	08/2023

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP150

Description

Regorafenib (Stivarga) is an orally administered kinase inhibitor acting on various membrane-bound and intracellular kinases.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
regorafenib (Stivarga)	Gastrointestinal stromal tumor, locally advanced, unresectable or metastatic disease after treatment with imatinib and sunitinib; Colorectal cancer, metastatic, previously treated with fluoropyrimidine, oxaliplatin, and irinotecan-containing chemotherapy, an anti-VEGF therapy, and if RAS wild type an anti-EGFR therapy; Hepatocellular (liver) carcinoma, previously treated with sorafenib	40 mg tablets	84 tablets/28 days

Initial Evaluation

- I. **Regorafenib (Stivarga)** may be considered medically necessary when the following criteria below are met:
 - A. Member is 18 years of age or older; **AND**
 - B. Medication is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
 - C. Medication is **not** used in combination with any other oncolytic medication (i.e., used as monotherapy); **AND**
 - D. A diagnosis of one of the following:
 1. **Colorectal Cancer; AND**
 - i. The member has metastatic (stage IV) disease; **AND**
 - ii. The member has previously progressed on or after a chemotherapy regimen history of all of the following:
 - a. fluoropyrimidine [e.g., capecitabine, fluorouracil (5-FU)]
 - b. oxaliplatin
 - c. irinotecan-containing chemotherapy; **AND**

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- iii. The member has previously progressed on or after an anti-VEGF therapy [e.g., bevacizumab (Avastin)]; **AND**
 - iv. The member has KRAS-mutated colorectal cancer; **OR**
 - a. If KRAS wild-type, the member has been treated with an anti-EGFR therapy [e.g., cetuximab (Erbix), panitumumab (Vectibix)]; **OR**
 - 2. **Gastrointestinal Stromal Tumor; AND**
 - i. The member has locally advanced (stage III), unresectable or metastatic (stage IV) disease; **AND**
 - ii. The member has previously progressed on or after imatinib (Gleevec); **AND**
The member has previously progressed on or after sunitinib (Sutent); **OR**
 - 3. **Hepatocellular Carcinoma; AND**
 - i. Provider attests the patient has Child-Pugh class A; **AND**
 - ii. The member has previously progressed on or after sorafenib (Nexavar)
- II. Regorafenib (Stivarga) is considered investigational when used for all other conditions, including but not limited to:
- A. Biliary cancer, cholangiocarcinoma
 - B. Esophagogastric cancer (esophageal, gastroesophageal, gastric)
 - C. Non-small cell lung cancer
 - D. Renal cell carcinoma
 - E. Soft tissue sarcoma
 - F. Adenoid cystic carcinoma
 - G. Urothelial carcinoma
 - H. Ovarian cancer
 - I. Osteosarcoma

Renewal Evaluation

- I. Member has received a previous prior authorization for this agent through this health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Regorafenib (Stivarga) will **not** be used in combination with other oncolytic medications (i.e., will be used as monotherapy); **AND**
- IV. Documentation of clinical response to therapy, such as stabilization of disease or decrease in tumor size or spread.

Supporting Evidence

- I. Regorafenib (Stivarga) has not been evaluated in patients under the age of 18; therefore, its safety and efficacy in the pediatric population is unknown.
- II. Due to the complex nature of treating any of the diagnoses regorafenib (Stivarga) is approved for, treatment should be prescribed by, or in consultation with, an oncologist.

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- III. Regorafenib (Stivarga) was evaluated in a randomized (2:1), double-blind, placebo-controlled study, the CORRECT trial, in adults with metastatic colorectal cancer after failure of standard therapy. The trial included 760 subjects, 505 in the regorafenib arm and 255 in the placebo arm, that had been previously treated with fluoropyrimidine-, oxaliplatin, and irinotecan-based chemotherapy, as well as bevacizumab (Avastin). All but one subject with KRAS wild-type disease received ANTI-EGFR therapy [cetuximab (Erbix), panitumumab (Vectibix)]. Regorafenib (Stivarga) showed a statistically significant improvement in overall survival (OS) compared to placebo [6.4 months vs. 5 months; HR 0.77 (CI 0.64-0.94), $p = 0.0102$].
- IV. The safety and efficacy of regorafenib (Stivarga) for gastrointestinal stromal tumors (GIST) was evaluated in a randomized (2:1), double-blind, placebo-controlled trial (GRID) in adults with unresectable, locally advanced or metastatic disease. A total of 199 patients, 133 in the regorafenib arm and 66 in the placebo arm, had been previously treated with imatinib (Gleevec) and sunitinib (Sutent). The medication showed a statistically significant improvement in progression-free survival (PFS) [PFS was 4.8 vs. 0.9 months; HR 0.27 (0.19-0.39), $p < 0.0001$]; however, there was no statistical difference in OS. This may have been influenced by cross-over to active therapy after disease progression on placebo as patients were allowed to change to regorafenib after progression and 56 of the 66 patients moved to the treatment arm.
- V. The clinical safety and efficacy of regorafenib (Stivarga) was evaluated in a randomized (2:1), double-blind, placebo-controlled trial (RESORCE) in adults with hepatocellular carcinoma, Child-Pugh class A. All subjects (379 in the regorafenib arm and 194 in the placebo, 573 total) had documented disease progression on sorafenib (Nexavar), and those that had discontinued sorafenib (Nexavar) due to toxicity rather than disease progression were ineligible for the trial; thus, safety and efficacy with regorafenib (Stivarga) prior to progression on or after sorafenib (Nexavar) has not been established. Overall survival was the primary outcome and was statistically significant in favor of regorafenib (Stivarga) over placebo [10.6 vs. 7.8 months; HR 0.63 (0.5-0.79), $p < 0.0001$].
- VI. In the clinical trials, severe drug-induced liver injury with fatal outcomes did occur. In the CORRECT study, fatal hepatic failure occurred in 1.6% of patients in the regorafenib arm and in 0.4% of patients in the placebo arm. In the GRID study, fatal hepatic failure occurred in 0.8% of patients in the regorafenib arm. In the RESORCE study, there was no increase in the incidence of fatal hepatic failure as compared to placebo. These drug-induced injuries were typically high-grade elevation of bilirubin, AST, ALT, and ALP with risk of developing injury roughly two-fold in the regorafenib arms compared to placebo.
- VII. As regorafenib was only studied in Child-Pugh class A (patients in the lower risk/best survival chances), safety of regorafenib in patients with Child-Pugh class B7 or beyond is unknown with the possibility of drug toxicity with worsening overall outcomes. Additionally, a clinical outreach to a key opinion leader (KOL) specializing in the treatment of liver cancer, agreed that use of regorafenib should be considered after failure of sorafenib, and only in patients with Child-Pugh class A liver status, as they have the best outcomes for a favorable prognosis while balancing the risk of treatment-induced hepatotoxicity. Additionally, the KOL expert noted that the best approach to the management of HCC patients with Child-Pugh class B7 or beyond may be via clinical trial enrollment or a liver transplant.
- VIII. For all indications regorafenib (Stivarga) is dosed at 160 mg per day on days 1-21 of each 28-day cycle. Product availability is 40 mg tablets and for patients experiencing dose-dependent

intolerance (adverse reactions), the dose of regorafenib (Stivarga) should be reduced in 40mg increments, with the lowest recommended dose of 80mg/day.

Investigational or Not Medically Necessary Uses

- I. Regorafenib (Stivarga) has not been sufficiently studied for safety or efficacy and/or is currently being evaluated in clinical trials for the following indications:
 - A. Osteosarcoma
 - i. First-line therapy for osteosarcoma is surgically removing the tissue/bone involved (either limb-sparing or limb-amputation) with radiation therapy followed by chemotherapy - based on the type and affected site of osteosarcoma (chondrosarcoma, Ewing sarcoma, Giant Cell Tumor of bone, etc.). Recommended systemic therapy options in this setting are: pembrolizumab (Keytruda), dasatinib (Sprycel), pazopanib (Votrient) or cisplatin/doxorubicin or MAP (high-dose methotrexate, cisplatin, and doxorubicin).
 - ii. The NCCN panel updated guidelines to give regorafenib a category 1 recommendation for second-line therapy for osteosarcoma (relapsed, refractory, or metastatic disease), based on the following data of two phase 2 clinical trials (REGOBONE and SARCO24) noting that regorafenib displayed antitumor activity in progressive metastatic osteosarcoma, delaying disease progression. However, at this time, regorafenib has not received FDA approval for the treatment of osteosarcoma.
 - iii. In the REGOBONE study, the primary endpoint was the number of patients without disease progression at 8 weeks. Patients were randomly assigned 2:1 to regorafenib or placebo with 38 patient total in the end efficacy analysis. 17 of 26 patients in the regorafenib arm (65%) were non-progressive at 8 weeks compared with 0 patients in the placebo arm. Although a preliminary indicator of efficacy, these results were not statistically significant, neither the study powered to evaluate the difference between the treatment and placebo arms.
 - iv. In the SARCO24 (randomized, double-blind, phase 2 study), progression free survival (PFS) was the primary endpoint. SARCO24 had 42 patients randomized 1:1 to regorafenib or placebo with allowance of crossover at time of disease progression. Median PFS was significantly improved with regorafenib versus placebo: 3.6 months (95% CI, 2.0 to 7.6 months) versus 1.7 months (95% CI, 1.2 to 1.8 months), respectively (hazard ratio, 0.42; 95% CI, 0.21 to 0.85; p 0.017). In the context of the crossover design, there was no statistically significant difference in overall survival. Additionally, based on consensus recommendations from the clinical experts, a progression-free survival (PFS) of ≥ 4 months has been regarded as a clinically meaningful metric of positive outcomes in the setting of osteosarcoma, which this trial did not attain.
 - B. Biliary cancer, cholangiocarcinoma
 - C. Esophagogastric cancer (esophageal, gastroesophageal, gastric)
 - D. Non-small cell lung cancer
 - E. Renal cell carcinoma

- F. Soft tissue sarcoma
- G. Adenoid cystic carcinoma
- H. Urothelial carcinoma
- I. Ovarian cancer

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3. Van Cutsem E., Sobrero AF., Siena S., et al. Phase III CORRECT trial of regorafenib in metastatic colorectal cancer (mCRC). *J Clin Oncol*. 2012: 2502.
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10. NCCN Clinical Practice Guidelines in Oncology: Hepatobiliary Cancers Version 5.2021 Available at: <https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1438>
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Related Policies

Policy Name	Disease state
Avapritinib (Ayvakit)	Unresectable or metastatic gastrointestinal stromal tumor with PDGFRA exon 18 mutation
Cabozantinib (Cabometyx, Cometriq)	Progressive or metastatic hepatocellular carcinoma, in patients previously treated with sorafenib
Dasatinib (Sprycel)	Gastrointestinal Stromal Tumors (GIST)
Encorafenib (Braftovi), binimetinib (Mektovi)	Metastatic colorectal cancer, with BRAF V600E mutation, combination therapy
Ripretinib (Qinlock)	Gastrointestinal Stromal Tumor, advanced disease after treatment with three or more tyrosine kinase inhibitors
Sunitinib (Sutent)	Gastrointestinal stromal tumor

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Trifluridine/tipiracil (Lonsurf)	Colorectal cancer-metastatic, previously untreated
Multi-Targeted Tyrosine Kinase Inhibitors (Multi-TKI)	Unresectable hepatocellular carcinoma

Policy Implementation/Update:

Action and Summary of Changes	Date
Added in Child-Pugh class A to hepatocellular cancer requirement based on KOL, NCCN, and clinical trial recommendations. Updated supporting evidence for the three FDA indications.	08/2022
Removed split fill	01/2022
Prior authorization transitioned to policy format. Addition of age edit, addition of monotherapy requirement. Renewal criteria transitioned to current formatting and language and increase from three to 12 month approval.	11/2019
Previous Reviews	01/2013; 02/2013; 04/2014; 09/2014;

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP228

Description

Relugolix is an orally administered gonadotropin-releasing hormone (GnRH) antagonist.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
relugolix (Orgovyx)	120 mg tablets	Prostate cancer	Initial: 30 tablets/28 days for one month Maintenance: 30 tablets/30 days

Initial Evaluation

- I. **Relugolix (Orgovyx)** may be considered medically necessary when the following criteria are met:
 - A. Member is 18 years of age or older; **AND**
 - B. Medication is prescribed by, or in consultation with, an oncologist or urologist; **AND**
 - C. A diagnosis of **prostate cancer**; **AND**
 1. Provider attestation the member is castration sensitive; **AND**
 2. Prostate cancer is advanced or metastatic (Stage III or IV); **AND**
 3. Treatment with a GnRH agonist (e.g., leuprolide [Lupron]), has been ineffective, not tolerated, or all GnRH agonists are contraindicated; **OR**
 - i. The member has a history of a major adverse cardiovascular event (MACE) (e.g., myocardial infarction, stroke); **AND**
 4. Degarelix (Firmagon) has been ineffective, not tolerated, or is contraindicated; **AND**
 - D. Relugolix (Orgovyx) is medically necessary for the treatment of prostate cancer over GnRH agonists and degarelix (Firmagon) [[documentation of medical necessity is verified by a clinical pharmacist at the health plan](#)]. (Note – preference for oral administration or other convenience does not meet medical necessity)
- II. Relugolix is considered investigational when used for all other conditions, including but not limited to:
 - A. Castration-resistant prostate cancer

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If so, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
 - A. Documentation of disease response to treatment (e.g., stabilization of disease or decrease in tumor size or tumor spread, reduction in serum testosterone or PSA); **OR**
 - B. Provider attestation that continuation of therapy is necessary if the member has had disease progression

Supporting Evidence

- I. Relugolix (Orgovyx) is a gonadotropin-releasing hormone (GnRH) receptor antagonist, FDA-approved for the treatment advanced prostate cancer. A 360 mg loading dose (three tablets) is administered on day one, then a maintenance dose of 120 mg (one tablet) is taken once daily. It is one of several androgen deprivation therapies (ADT) available. Other options include GnRH agonists such as leuprolide (Lupron), goserelin (Zoladex), triptorelin (Telstar/Triptodur), histrelin (Supprelin LA, Vantas), and GnRH agonist [degarelix (Firmagon)], all of which are injectable medications. Additionally, surgical orchiectomy is an option when prompt castration is required. Reducing serum testosterone to castrate levels is warranted for the treatment of prostate cancer, and all of these methods are highly effective. Androgen deprivation therapy is a hallmark of treatment, and is generally continued, if tolerated, even if there is progressive disease and/or if other prostate cancer medications are started. Given the specialization of the condition and treatment options, therapy should be prescribed by, or in consultation with, an oncologist.
- II. The GnRH agonists are highly utilized for the treatment of advanced or metastatic prostate cancer. They are known to cause a testosterone surge upon initiation, with a subsequent decrease in serum testosterone three-to-four weeks after starting treatment. For patients at risk for these symptoms, an antiandrogen therapy (e.g., flutamide, nilutamide, bicalutamide) may be administered concurrently for the first few weeks of GnRH agonist treatment. Some agents are available in every-three-month injections and are generally well tolerated
- III. The GnRH antagonists, degarelix (Firmagon), and now relugolix (Orgovyx), are successful at mitigating the testosterone surge and may rapidly reduce testosterone; although, the rapidity of testosterone suppression with GnRH antagonists has not been linked to superior clinical benefit over the GnRH agonists in the general population likely to utilize these therapies.
- IV. Relugolix (Orgovyx) was evaluated in one Phase 3, randomized, open-label, non-inferiority (NI) trial vs. leuprolide (Lupron) over 48 weeks in patients with advanced or metastatic disease. Up to 13% of patients had previous ADT, 30% had previous radiotherapy, and 14% had a history of major adverse cardiovascular event (MACE). There was a washout period of three months for those previously treated with degarelix (Firmagon) and one year for those on GnRH agonist therapy. Those with a MACE in the six months before the trial were excluded. All patients included in the trial were adults, which is the expected population to be diagnosed with prostate

- cancer. At this time the safety and efficacy of relugolix (Orgovyx) in pediatric patients remains unknown; however, it would be very rare for a pediatric patient to develop prostate cancer.
- V. The primary outcome was cumulative sustained castration rate of less than 50 ng/dL from day 29 through 48 weeks. Results were 96.7% of patients for relugolix (Orgovyx) and 88.8% for leuprolide (Lupron), with a difference of 7.9% (CI 4.1-11.8). Additionally, a notable secondary outcome was castration relapse free survival (CRFS) at 48 weeks. This was 74% for relugolix (Orgovyx) and 75% for leuprolide (Lupron) (HR 1.03, CI 0.68-1.57, p=0.84). Both of these outcomes showed NI of relugolix (Orgovyx) to leuprolide (Lupron). Statistically, relugolix (Orgovyx) was superior to leuprolide (Lupron) in the primary outcome; however, both therapies showed a very high rate of sustained castration. At this time definitive data are lacking to indicate clinical superiority of either product in regard to medication efficacy.
 - VI. There were several other secondary outcomes measured: probability of testosterone suppression to less than 50 ng/dL on day four and day 15, prostate specific antigen (PSA) response on day 15 and day 29, probability of profound testosterone suppression (less than 20 ng/dL) on day 15. These were all superior for relugolix (Orgovyx) over leuprolide (Lupron). This is expected given the mechanistic differences of the therapies. Given the known initial testosterone surge with GnRH agonists, castrate levels would be expected three-to-four weeks after medication initiation. The results confirm the rapidity of testosterone suppression for relugolix (Orgovyx), as expected for a GnRH antagonist.
 - VII. Rate of overall adverse events (AE) was consistent across both groups. Common AE (greater than 10%) that occurred in both groups included laboratory abnormalities, increase glucose levels, increase triglycerides, musculoskeletal pain, increased hemoglobin, ALT/AST increases, constipation, and diarrhea.
 - VIII. Serious AE occurred in 9.8% of the relugolix (Orgovyx) group, and 15.3% of the leuprolide (Lupron) group. For relugolix (Orgovyx) sAE: myocardial infarction (0.8%), AKI (0.6%), hemorrhage (0.6%), and UTI (0.5%).
 - IX. The MACE rate was 2.9% for relugolix (Orgovyx) and 6.2% for leuprolide (Lupron), overall. This was further pronounced in the subgroup of patients that had a previous MACE. Rates were 3.6% and 17.8%, respectively. In the group without a previous MACE, rates were 2.8% and 4.2%, respectively. From the data, it is predicted that GnRH antagonists may have a favorable safety profile in those with history of a MACE, such as myocardial infarction and stroke. Options include degarelix (Firmagon) as well as relugolix (Orgovyx), and current data are lacking to indicate clinical favorability between these two agents.

Investigational or Not Medically Necessary Uses

- I. Relugolix has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Castration-resistant prostate cancer

References

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy

Policy Name	Disease state
GnRH Antagonists in Gynecologic Conditions	Heavy menstrual bleeding associated with uterine fibroids (leiomyoma) Moderate to severe pain associated with endometriosis
Gonadotropin-releasing hormone (GnRH)	Endometriosis, Central Precocious Puberty (CPP), Advanced Prostate Cancer, Uterine leiomyoma (fibroids), Advanced breast cancer in premenopausal women, Reduction of endometrial thickness prior to endometrial ablation, Gender Dysphoria

Policy Implementation/Update:

Action and Summary of Changes	Date
Myfembree moved to GnRH Antagonists in Gynecologic Conditions policy for uterine fibroids and moderate to severe pain with endometriosis; Endometriosis removed from E/I section; Changed policy name to relugolix (Orgovyx)	11/2022
Policy created	05/2021

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP117

Description

Repository corticotropin injection (Acthar, Cortrophin) gel is an adrenocorticotrophic hormone (ACTH) analogue that stimulates the adrenal cortex to secrete cortisol, corticosterone, aldosterone, and other weak androgenic substances.

Length of Authorization

- Initial: One month
- Renewal: One month, total of two courses allowed per lifetime (i.e., one renewal allowed).

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
repository corticotropin injection (Acthar Gel and Acthar Gel SelfJect™)	Infantile Spasms (West Syndrome)	80 units/mL vial (400 units/5mL)	Monthly quantity in mL to allow for: 150 u/m ² daily for two weeks plus a two-week taper as follows: three days' worth of 30 u/m ² , three days' worth of 15 u/m ² , six days' worth of 10 u/m ²
	Multiple sclerosis, rheumatic disorders, collagen diseases, dermatologic diseases, allergic states (serum sickness), ophthalmic diseases, respiratory diseases, edematous state	40 units/0.5 mL or 80 units/mL single dose autoinjector*	1 injection/day
repository corticotropin injection (Purified Cortrophin Gel)	Infantile Spasms (West Syndrome)	80 units/mL vial (400 units/5mL)	Monthly quantity in mL to allow for: 150 u/m ² daily for two weeks plus a two-week taper as follows: three days' worth of 30 u/m ² , three days' worth of 15 u/m ² , six days' worth of 10 u/m ²
repository corticotropin injection (Purified Cortrophin Gel SQ PFS)		40 units/0.5mL	1 injection/day
		80 units/0.5mL	1 injection/day

*All indications for the Acthar Gel SelfJect™ autoinjector are considered not medically necessary. This product is NOT approved for infantile spasms.

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Initial Evaluation

- I. **Repository corticotropin (Acthar Gel vial)** may be considered medically necessary when the following criteria below are met:
 - A. Medication is prescribed by, or in consultation with, a neurologist; **AND**
 - B. A diagnosis of one of **Infantile Spasms (West Syndrome)**; **AND**
 1. Member is under two years of age; **AND**
 2. Medication to be used as monotherapy; **AND**
 3. Documentation of recent body surface area; **OR**
 - i. Documentation of member's height and weight (needed for dose calculation).; **OR**
- II. **Repository corticotropin (Purified Cortrophin Gel)** may be considered medically necessary when the following criteria below are met:
 - A. Criteria I(A)-I(B) above have been met; **AND**
 1. Documentation that treatment with repository corticotropin injection (Acthar Gel) has been ineffective, not tolerated, or contraindicated.
- III. Repository corticotropin (Acthar Gel and Acthar Gel SelfJect™) and Repository corticotropin (Purified Cortrophin Gel) are considered not medically necessary when criteria above are not met and/or when used for the following:
 - A. Multiple sclerosis
 - B. Rheumatoid arthritis
 - C. Psoriatic arthritis
 - D. Ankylosing spondylitis
 - E. Dermatomyositis/polymyositis
 - F. Optic neuritis (40 units daily, also included in investigational section for other doses, see below)
 - G. For use in nephrotic syndrome over corticosteroid therapy (also included in investigational section, see below)
- IV. Repository corticotropin (Acthar Gel and Acthar Gel SelfJect™) and Repository corticotropin (Purified Cortrophin Gel) are considered investigational when used for all other conditions, including but not limited to:
 - A. In combination with anti-epileptic therapies for the treatment of infantile spasms (West Syndrome)
 - B. Ophthalmic conditions and diseases: keratoconjunctivitis sicca, Sjogren's syndrome, dry eye disease, keratitis, iritis, iridocyclitis, uveitis, choroiditis, optic neuritis, etc.
 - C. Nephrotic syndrome (NS) and NS due to focal segmental glomerulosclerosis (FSGS) or immunoglobulin A nephropathy (IgAN)
 - D. Juvenile rheumatoid arthritis
 - E. Lupus erythematosus
 - F. Dermatologic conditions: erythema multiforme, Steven's Johnson syndrome
 - G. Serum sickness
 - H. Sarcoidosis

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. A diagnosis of one of **Infantile Spasms (West Syndrome)**; **AND**
 - A. Member is under two years of age; **AND**
 - B. Medication to be used as monotherapy; **AND**
 - C. Documentation of recent body surface area; **OR**
 - a. Documentation of member's height and weight (needed for dose calculation); **AND**
- IV. The member has been previously treated successfully with an initial treatment course of repository corticotropin (Acthar, Cortrophin) gel (i.e., improvement in seizures); **AND**
- V. The member has relapsed, and a second course of therapy is warranted; **AND**
- VI. The member has not yet received a total of two or more courses of therapy in their lifetime.

Supporting Evidence

- I. **Infantile spasms (West Syndrome):** Repository corticotropin (Acthar) gel is an ACTH analogue that acts similarly to corticosteroids and was FDA-approved for infantile spasms in 2010. Data from several randomized controlled trials are available to support safety and efficacy. One clinical trial showed superiority over prednisone in the proportion of patient responders to therapy. Other studies directly comparing therapy to corticosteroids did not determine statistical superiority of repository corticotropin (Acthar) gel. Although data for superiority of repository corticotropin (Acthar) gel over corticosteroids are conflicting, there is insufficient evidence to support that corticosteroids could be more effective than repository corticotropin (Acthar) gel. Guidelines recommend repository corticotropin (Acthar) as the mainstay therapy.
 - Infantile spasms are characterized as epileptic spasms that appear in infancy and early childhood. The majority of patients will present before seven months of age, and the condition is associated with electroencephalographic pattern of hypsarrhythmia. This medication has been evaluated and is only FDA-approved for patients under two years of age. In patients older than two years, alternative cost-effective treatment options should be considered.
 - In clinical practice, repository corticotropin (Acthar) gel has been utilized at a variety of doses. The FDA-approved dose (which has also been evaluated in several clinical trials) is as follows: 150 units/m² daily (divided between twice daily) for two weeks plus a two-week taper: three days each of 30 units/m², 15 units/m², 10 units/m², followed by 10 units/m² every other day for six days. The last six days of therapy equates to total of three additional days of 10 units/m² (equating to six full days of the 10 units/m² dose). Several studies have evaluated differing dosing regimens, including lower doses. In the event under dosing is prescribed relative to the FDA-approved dose, this regimen should be allowed given some evidence to indicate that lower doses may be as effective as that FDA-approved. Repository corticotropin (Acthar) gel has been

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evaluated in clinical trials using 150 units/m² for three weeks then a taper for three more weeks; however, this higher dose group did not show superior efficacy to lower doses. Similar rates of response and relapse occurred; thus, at this time there is no evidence to support need for a longer than two-week duration of 150 units/m² per day.

- Duration of initial therapy with treatment and taper is four weeks. Response is expected in the first few weeks. There is lack of evidence to support extended use of therapy; however, a second course of therapy may be appropriate for patients that relapse and require retreatment. Lack of response (i.e., number/severity of spasms) on first treatment course signals an alternative regimen should be utilized for retreatment; thus, response to the initial therapy course is required. Long-term safety is similar to corticosteroids: cardiac, ocular, mood, sleep, skin concerns, etc.
- Repository corticotropin (Cortrophin) gel is not FDA-approved for the indication of infantile spasms; however, is not expected to have any clinical differences. This is a more cost-effective treatment option, and when other criteria are met for the indication of infantile spasms, Cortrophin use is covered under the specifications listed above (e.g., QLL, etc.). ANI Pharmaceuticals received FDA-approval of Purified Cortrophin gel in November 2021, in efforts to support broader and more cost-effective access to corticotropin products.

- II. Repository corticotropin (Acthar) gel was FDA-approved in 1952 and Cortrophin gel was approved in 1954 for the treatment of inflammatory conditions prior to current FDA standards, and the indications were grandfathered into the labels; however, corticotropin products have not demonstrated evidence for safety and efficacy, or medical necessity over corticosteroids, for the majority of the labeled indications. Furthermore, the cost has increased significantly over the past few decades: \$36 per vial in 2001; in 2022, \$49,750 per vial for Acthar and \$38,200 for Cortrophin. The evidence for indications outside of infantile spasms and multiple sclerosis (MS) are absent, are low quality and/or lacking ability to conclude efficacy and safety alone or in comparison to more cost-effective therapies (e.g., corticosteroids). Data to support efficacy for indications other than infantile spasms are absent from the prescribing information label. The manufacturer of Acthar, Mallinckrodt has funded several Phase 4 clinical trials in recent years in efforts to provide support for the approved indications; however, by in large these clinical trials are insufficient to support the safety and efficacy and/or medical necessity over other therapies.

Investigational or Not Medically Necessary Uses

- I. Repository corticotropin (Acthar, Cortrophin) (ACTH) gel is considered not medically necessary for the following conditions:
- A. Multiple sclerosis: At this time, it is unproven if ACTH gel is more likely to provide similar therapeutic results or is superior to other corticosteroids, given lack of quality trials and trials with consistent results showing superiority; however, ACTH gel is more costly than other therapies that could be utilized. Given these factors ACTH gel is not medically necessary for MS and is not covered. Furthermore, choice of or success of therapy in acute MS exacerbation has not been correlated with improved or superior long-term outcomes, further reducing the necessity of ACTH gel for this condition.
 - B. Rheumatoid arthritis, psoriatic arthritis, dermatomyositis/polymyositis, ankylosing spondylitis: ACTH gel has been evaluated in Phase 4, randomized, placebo-controlled

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withdrawal studies for these conditions in addition to several lesser quality trials. In some trials, therapy was superior to placebo for disease response; however, this medication has not been directly compared to NSAIDs, the majority of systemic corticosteroids, conventional synthetic DMARDs, specialty DMARDs, and biologic therapies. Numerous other medications have strong evidence for safety and efficacy, all of which are more cost-effective. At this time, it is unproven if ACTH gel is more likely to produce similar therapeutics results or is superior to other therapies; however, ACTH gel is more costly than other therapies that could be utilized. Furthermore, ACTH gel is not recognized as an appropriate therapy per guidelines or standard practice; thus, is considered not medically necessary and is not covered.

- C. Optic neuritis (also considered experimental and investigational, see below): ACTH gel was evaluated in one RCT vs. placebo, where 40 units daily for 30 days did not provide significant changes over placebo in visual acuity and visual field scores. Given that it is not known if therapy improves therapeutic outcomes at this dose, ACTH gel is considered not medically necessary and is not covered.
 - D. Nephrotic syndrome: superiority of ACTH gel over corticosteroids and other treatment options for this condition has not been demonstrated; certain trials have shown lack of benefit over placebo therapy and one clinical trial showed noninferiority to methylprednisolone. At this time, it is unproven if ACTH gel is more likely to provide similar therapeutic results or is superior to other corticosteroid therapies; however, ACTH gel is more costly than other therapies that could be utilized. Given these factors ACTH gel is not medically necessary and is not covered.
- II. Repository corticotropin (Acthar, Cortrophin) gel has not been sufficiently studied for safety and efficacy, and are considered experimental and investigational, for the following conditions or settings below:
- A. In combination with anti-epileptic therapies for the treatment of infantile spasms (West Syndrome): ACTH gel has only been evaluated as monotherapy for the treatment of infantile spasms. There is unknown safety and efficacy when utilized for other anti-epileptic medications. When combination therapy is indicated vigabatrin plus corticosteroids may be considered as available evidence for efficacy and safety.
 - B. Systemic lupus erythematosus (SLE): Evaluated in a single-arm, open-label, four-week trial in 10 patients. This trial does not provide any certainty in the benefit of ACTH gel for SLE given the significant trial biases: subjective outcomes in an open-label trial, no comparator to be able to determine extent of benefit over placebo (if any), few patients evaluated, and concomitant medications which may have impacted/influenced the changes.
 - C. Optic neuritis (ON) (higher doses): Evaluated in a single-arm, open-label, 2-week trial at a starting dose of 80 units daily in 24 patients with ON. This trial does not provide any certainty in the benefit of therapy for ON given the significant biases in the trial: subjective outcomes in an open-label trial, few patients evaluated, short trial duration, and patients were on background therapies at the start of the trial, with no washout period. Results/conclusions seen in this assessment may not be attributable to ACTH gel.
 - D. Sarcoidosis: Evaluated for sarcoidosis in one retrospective medical record review, on provider assessment of “patients’ health status”. The trial showed that use of concomitant medications such as glucocorticoids decreased with use of ACTH gel. This trial does not

provide any certainty in the benefit of therapy for this condition given the significant biases: retrospective trial design, subjective and invalidated outcomes in a nonblinded trial, most patients were on background therapies. Results/conclusions seen in this assessment may not be attributable to ACTH gel.

- E. Nephrotic Syndrome (NS), including but not limited to those with FSGS: Evaluated in retrospective case series; a prospective, open-label, single arm trial, a randomized noninferiority trial vs. methylprednisolone with cytotoxic therapies; a randomized, placebo-controlled trial; a dose comparison trial; and one Cochrane systematic review evaluated in one retrospective case series in 44 patients (15 patients had FSGS). Data are heavily conflicting, none of which strongly point to medication benefit. For example, one of the randomized controlled trials showed no substantial differences compared to no therapy and the trial was ended early for no benefit. In the noninferiority trial, similar responses were seen to methylprednisolone. The Cochrane review determined lack of sufficient data to draw conclusions of efficacy and safety. The collection of data does not provide certainty of benefit of therapy for NS, is considered experimental and investigational, and is not covered by the health plan. At this time, it is also unproven if ACTH gel is more likely to provide similar therapeutic results or is superior to other corticosteroid therapies; however, ACTH gel is more costly than other therapies that could be utilized. Thus, ACTH gel is also not medically necessary over corticosteroids and is not covered.
 - i. NS due to immunoglobulin A nephropathy (IgAN): ACTH gel was evaluated in a single-arm, open-label pilot study in 19 patients. This trial does not provide any certainty in the benefit of therapy for this condition given the significant biases in the trial, including but not limited to small number of patients in the trial, lack of comparator arm, and the majority of outcomes were unchanged at follow-up.
- F. Ophthalmic conditions and diseases, including but not limited to: keratoconjunctivitis sicca, Sjogren's syndrome, dry eye disease, keratitis, iritis, iridocyclitis, uveitis, choroiditis:
 - i. Keratitis/dry eye disease: ACTH gel was evaluated in a single-arm, open-label study in 35 patients with keratitis. The trial observed 12-point change in IDEEL score for 17 patients (50%) with severe keratitis. ACTH gel was also evaluated in a single-arm, open-label pilot study in dry eye disease in 15 patients. The study evaluated the SANDE questionnaire for patient reported improvement; however, these trials do not provide any certainty in the benefit of therapy for this condition given the significant biases in the trial, including but not limited to subjective outcomes in an open-label trial, lack of comparator, the small number of patients evaluated, and background or concomitant therapies may not have been reported so any results or conclusions may not be attributable to ACTH gel. Furthermore, the SANDE score is not a validated measurement tool for clinically meaningful change in dry eye comfort or symptom improvement.
 - 1. Alternative therapies and management strategies include, but may not be limited to: avoidance of offending medications, environmental management, moisture conserving eyewear, ocular lubricants, artificial tears and preservative-free artificial tears (gels, ointments, drops), ophthalmic cyclosporine (generic, Restasis, Cequa), ophthalmic lifitegrast

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- (Xiidra), nasal varenicline (Tyrvaya), punctal plugs or occlusion, topical steroids, therapeutic contact lenses, autologous serum tear preparations.
- ii. Uveitis: ACTH gel has been evaluated for uveitis in one retrospective trial evaluating medical record data of provider assessment on patients' health status for 91 patients. Trial conclusions were that provider reported improved patient status; however, this trial does not provide any certainty in the benefit of therapy for this condition given the significant biases in the trial, including but not limited to subjective outcomes in an open-label trial, lack of comparator, the small number of patients evaluated, and background or concomitant therapies were utilized by 100% of patients (including steroid eye drops, oral steroids, intraocular steroids, and non-steroid eye drops) so any results or conclusions may not be attributable to ACTH gel.
- III. Juvenile rheumatoid arthritis
 - IV. Dermatologic conditions: erythema multiforme, Steven's Johnson syndrome
 - V. Serum sickness
 - VI. Sarcoidosis

Appendix

- I. Methods to calculate body surface area include, but are not limited to the Mosteller method: $BSA (m^2) = \text{Square root } ((Ht (cm) \times Wt (kg))/3600)$

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Related Policies

Currently, there are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
Added repository corticotropin injection (Purified Cortrophin Gel SQ PFS) to policy	03/2025
Added Acthar Gel Selfject™ to policy/QL table.	09/2024
Updated criteria to require an inadequate response, intolerance, or contraindication to repository corticotropin (Acthar Gel) prior to repository corticotropin (Purified Cortrophin Gel), effective 10/01/2022	09/2022
Policy criteria updated for infantile spasms indication: removal of congenital infection rule out, addition of body surface (or height and weight) requirement for dose calculation. Change of renewal criteria to check	06/2022

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that patients still meet initial requirements and that member has had a response to therapy that would predict response with a retreatment. Criteria updated to allow for maximum of two courses per lifetime. Supporting evidence updated for infantile spasms, not medically necessary and experimental and investigational designations and information added for supporting evidence. Addition of Cortrophin to policy. Formatting updates.	
Policy created	11/2019

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP304

Split Fill Management*

Description

Repotrectinib (Augtyro) is an orally administered selective tyrosine kinase inhibitor (TKI).

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
repotrectinib (Augtyro)	Advanced or metastatic ROS1-positive non-small cell lung cancer (NSCLC)	40 mg capsules	240 capsules/30 days
	Neurotrophic receptor tyrosine kinase (NTRK) gene fusion positive solid tumors	160 mg capsules	60 capsules/30 days

Initial Evaluation

- I. **Repotrectinib (Augtyro)** may be considered medically necessary when the following criteria are met:
 - A. Medication is prescribed by, or in consultation with, an oncologist; **AND**
 - B. Medication is not used in combination with any other oncology therapy; **AND**
 - C. A diagnosis of one of the following:
 1. **Non-small cell lung cancer (NSCLC); AND**
 - i. Member is 18 years of age or older; **AND**
 - ii. Confirmation of ROS1-positive mutation; **AND**
 - iii. The disease is advanced (Stage III); **OR**
 - iv. The disease is metastatic (IV); **AND**
 - a. There is no evident CNS metastases; **AND**
 - i. Treatment with entrectinib (Rozlytrek) or crizotinib (Xalkori) have been ineffective, contraindicated, or not tolerated; **OR**
 - b. There is CNS metastases; **AND**
 - i. Treatment with entrectinib (Rozlytrek) has been ineffective, contraindicated, or not tolerated; **OR**
 2. **Solid tumor; AND**
 - i. Member is 12 years of age or older; **AND**
 - ii. The disease is advanced (stage III), metastatic (stage IV), or unresectable; **AND**
 - iii. Confirmation of neurotrophic receptor tyrosine kinase (NTRK) gene fusion; **AND**
 - iv. Documentation of intolerance or contraindication to entrectinib (Rozlytrek)

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- v. Provider attestation that all alternative therapies for diagnosis and stage of cancer per compendia have been exhausted, as defined by:
 - a. Progression following all appropriate treatments; **OR**
 - b. Nonresponse to all available therapies; **OR**
 - c. All available therapies are contraindicated or not tolerated; **OR**
 - d. No standard or satisfactory treatment exist
- II. Repotrectinib (Augtyro) is considered investigational when used for all other conditions, including but not limited to:
 - A. NSCLC with other mutations (e.g. ALK, RET, BRAF, etc.)
 - B. Solid tumors with ROS1 rearrangement
 - C. Repotrectinib (Augtyro) used in combination with another oncology therapy
 - D. KRAS-mutant solid tumors

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise; **AND**
- III. Member has exhibited response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread; **AND**
- IV. Medication is not used in combination with any other oncology therapy

Supporting Evidence

- I. Repotrectinib (Augtyro) is a ROS1 tyrosine kinase inhibitor (TKI), FDA-approved for the treatment of adult patients with locally advanced or metastatic ROS1-positive non-small cell lung cancer (NSCLC) and neurotrophic receptor tyrosine kinase (NTRK) gene fusion positive solid tumors. Repotrectinib (Augtyro) is an oral capsule administered once daily for 14 days, then increased to twice daily thereafter.

Non-small cell lung cancer (NSCLC)

- II. Lung cancer is the second most common cancer diagnosed in the United States and the leading cause of cancer-related death. Non-small cell lung cancer represents up to 85% of lung cancer diagnoses. ROS1 fusions are rare and occur in about 1-2% of patients with NSCLC. The median age of diagnosis is 50 years old and ROS1 rearrangement is more common in females. ROS1 rearrangement tends to be more aggressive and there is an increased risk of G2032R mutations, which result in TKI resistance, and ultimately, fewer treatment options. Central nervous system metastases are the most common site of disease progression after development of TKI resistance. Given the complexity of management of mCRC, the treatment of mCRC must be initiated by, in or consultation with an oncologist.
- III. Repotrectinib (Augtyro) is the third FDA-approved TKI and joins entrectinib (Rozlytrek) and crizotinib (Xalkori) for treatment of ROS1-positive NSCLC. Repotrectinib (Augtyro) is the first TKI approval that includes patients with ROS1-positive non-small cell lung cancer who have previously received a ROS1 tyrosine kinase inhibitor, in addition to patients who are tyrosine kinase inhibitor naïve. Repotrectinib (Augtyro) will compete against entrectinib (Rozlytrek) and crizotinib (Xalkori) in the first- and second-line setting.

- IV. Repotrectinib (Augtyro) was studied in a Phase 1/2, international, multicenter, single arm, open label, multi cohort study which included 71 TKI-naïve participants who received up to one prior line of platinum-based chemotherapy and 56 participants who received 1 prior ROS1 TKI with no prior platinum-based chemotherapy. Participants received repotrectinib (Augtyro) 160mg once daily for 12 days, then 160mg twice daily. Baseline characteristics were similar between both cohorts: median age 57 years old, mostly female (>60%), of those ROS1 TKI-naïve, 72% of participants were also chemotherapy naïve, there was 24% brain metastases in the TKI-naïve group and 46% in the prior TKI group, and of those that had prior TKI therapy, 82% had received crizotinib. The primary endpoint, overall response rate (ORR), was 78% (n=56, 95% CI, 68-88) for the TKI-naïve cohort and 38% (n=56, 95% CI, 25-52) for the cohort with prior TKI. The median progression free survival (PFS) was 35.7 months (95% CI, 27.4-non-estimable) and 9.0 months (95%, 17.8-non-estimable) for the TKI-naïve and prior TKI cohorts, respectively. The median time to response was 1.8 months.
- V. The safety analysis was completed in all 426 participants of the Phase 2 pooled population, which included other genetic mutations (e.g. ALK, NTRK1-3, etc.). The most common adverse events included dizziness (58%), dysgeusia (50%), paresthesia (30%), constipation (26%), anemia (26%), and ataxia (20%). Adverse events led to dose reduction in 163 participants (38%), dose interruption in 213 participants (50%), and treatment discontinuation in 31 participants (7%).
- VI. There is moderate confidence that repotrectinib (Augtyro) provides an objective and meaningful difference in patients with NSCLC. Although there is low confidence in the single arm, open label study design, the trial has a similar study design and comparable efficacy endpoints to similar treatment options. Repotrectinib's (Augtyro) efficacy endpoints are promising as the duration of response and progression free survival are non-estimable and quality of life measures demonstrate an increase of ≥ 10 points at cycle 6 and stable scores throughout treatment.
- VII. The National Comprehensive Cancer Network (NCCN) guidelines have been updated to recommend entrectinib (Rozlytrek), crizotinib (Xalkori), and repotrectinib (Augtyro) as first and second line therapy for NSCLC with ROS1 fusion (category 2A, all preferred). After progression on therapy, if there is brain metastases, guidelines recommend entrectinib (Rozlytrek), repotrectinib (Augtyro), or lorlatinib (Lobrena) (category 2A). The TRIDENT-1 trial permitted participants to receive prior entrectinib (Rozlytrek) (N= 9, 16%) or crizotinib (Xalkori) (N= 46, 82%) and requiring step through these agents for metastatic disease is both clinically appropriate and cost-effective.

Solid tumor with a confirmed neurotrophic receptor tyrosine kinase (NTRK) gene fusion

- VIII. Neurotrophic tropomyosin kinase (NTRK) receptors are part of the transmembrane tyrosine kinases responsible for neuronal development. Although NTRK gene fusion is present in both adult and pediatric populations, it is less prevalent (<5%) in common tumor types like colorectal, breast, and lung adenocarcinomas. NTRK gene fusion is most prevalent (>90%) in rare forms of tumors, such as head and neck cancers (e.g., secretory mammary carcinoma and mammary analogue secretory carcinoma (MASC)), and rare forms of soft tissue sarcomas. Due to the rarity of NTRK gene fusion positive tumors, confirmation laboratories testing is required for diagnosis.
- IX. Repotrectinib (Augtyro) is the third FDA-approved TKI and joins entrectinib (Rozlytrek) and larotrectinib (Vitrakvi) for the treatment of NTRK gene fusion positive solid tumors that are locally advanced or metastatic or unresectable.
- X. Repotrectinib (Augtyro) was approved for treatment in NTRK gene fusion positive solid tumors under the accelerated pathway. Repotrectinib (Augtyro) was studied in a Phase 2, multicenter, single-arm, open-label, cohort expansion study (TRIDENT-1) in the setting of NTRK gene fusion positive tumors. The multi-cohort trial included 40 TKI-naïve participants and 48 TKI-pretreated participants. TKI-pretreated participants received up to two prior TKI therapies (e.g. entrectinib,

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larotrectinib, selitrectinib, or cabozantinib). Participants received repotrectinib (Augtyro) 160 mg once daily for 14 days, then 160 mg twice daily. The TKI-pretreated cohort had a higher proportion of participants who had at least one prior chemotherapy or immunotherapy systemic treatment regimen compared to the TKI-naïve cohort. The median age of participants was 61 years old in TKI-naïve cohort and 58 years old in the TKI-pretreated cohort. The proportion of Asian participants in TKI-naïve cohort was 53% and the proportion of White participants in TKI-pretreated cohort was 65%. The primary endpoint, overall response rate (ORR), was 58% (n=40, 95% CI, 41-73) for TKI-naïve cohort and 50% (n=48, 95% CI, 35-65) for TKI-pretreated cohort. The median duration of response (DOR) was not estimable in TKI-naïve cohort and 9.9 months (95% 7.4-13) for TKI-pretreated cohort.

- XI. The safety analysis for NTRK gene fusion positive solid tumors was completed in all 426 participants of the Phase 2 (TRIDENT-1) pooled population, which included other genetic mutations (e.g. ALK, ROS1-positive NSCLC, etc.). The most common adverse events included dizziness (58%), dysgeusia (50%), paresthesia (30%), constipation (26%), anemia (26%), and ataxia (20%). Adverse events led to dose reduction in 163 participants (38%), dose interruption in 213 participants (50%), and treatment discontinuation in 31 participants (7%).
- XII. Despite statistically significant outcomes, there are concerns with the use of surrogate primary and secondary endpoints, as they do not translate to clinical outcomes and a lack of a placebo or comparator arm to demonstrate true clinical effect. There is low confidence that repotrectinib (Augtyro) provides a clinically objective and meaningful difference in patients with NTRK positive solid tumors.
- XIII. The NCCN guidelines recommend different treatment options dependent on tumor type. For example, salivary gland cancers are among the most common solid tumors with NTRK fusion. In salivary gland cancers with NTRK fusion, NCCN recommends larotrectinib (Vitrakvi), entrectinib (Rozlytrek), and repotrectinib (Augtyro) (Category 2 recommendation) whereas the treatment recommendation is different for soft tissue cancers. The TRIDENT-1 trial permitted participants to receive prior entrectinib (Rozlytrek) prior to randomization and repotrectinib (Augtyro) is recommended as subsequent second line therapy after treatment with prior TKI (category 2a recommendation). Therefore, requiring step through these agents for metastatic disease is both clinically appropriate and cost-effective.

Investigational or Not Medically Necessary Uses

- I. There are ongoing clinical studies to assess efficacy and safety of repotrectinib (Augtyro) in other settings. Notably, clinical trials in the settings of NSCLC with other mutations are underway. Repotrectinib (Augtyro) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. NSCLC with other mutations (e.g. ALK, RET, BRAF, etc.)
 - B. Solid tumors with ROS1 rearrangement
 - C. Repotrectinib (Augtyro) used in combination with another oncology therapy
 - D. KRAS-mutant solid tumors

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
entrectinib (Rozlytrek®)	Neurotrophic receptor tyrosine kinase gene fusion positive solid tumors NSCLC, metastatic, ROS1-positive
ALK+ Inhibitors	NSCLC, metastatic, ALK-positive
	NSCLC, metastatic, ROS1- positive
	Recurrent, refractory, Inflammatory myofibroblastic tumors, ALK-positive, unresectable
	Relapsed, refractory systemic anaplastic large cell lymphoma, ALK-positive
encorafenib (Braftovi®), binimetinib (Mektovi®)	Malignant melanoma, unresectable or metastatic, with BRAF V600E or V600K mutation, combination therap
	Metastatic colorectal cancer, with BRAF V600E mutation, combination therapy
pralsetinib (Gavreto®)	RET Fusion-Positive Non-Small Cell Lung Cancer
sotorasib (Lumakras®)	Non-Small Cell Lung Cancer (NSCLC), advanced or metastatic with a KRAS G12C mutation

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated to include new indication for NTRK positive solid tumors in patients 12 years and older and new initial evaluation criteria. Addition of new strength formulation and quantity limit. Addition of new E/I indication. Updated supporting evidence.	02/2025
Policy created	05/2024

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP289

Description

Resmetirom (Rezdiffra) is a liver-targeted thyroid hormone receptor-beta (THR-β) selective agonist pending FDA-approval for the treatment of adults with nonalcoholic steatohepatitis (NASH) with liver fibrosis.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
resmetirom (Rezdiffra)	nonalcoholic steatohepatitis (NASH)/ Metabolic Dysfunction-Associated Steatohepatitis (MASH)	For weight < 100kg: 80 mg tablets	30 tablets/30 days
		For weight ≥100kg: 100 mg tablets	

Initial Evaluation

- I. **Resmetirom (Rezdiffra)** may be considered medically necessary when the following criteria are met:
 - A. Member is 18 years of age or older; **AND**
 - B. Medication is prescribed by, or in consultation with, a hepatologist or gastroenterologist; **AND**
 - C. Member has a diagnosis of **nonalcoholic steatohepatitis (NASH)/Metabolic Dysfunction-Associated Steatohepatitis (MASH)** when the following are met:
 1. Diagnosis is biopsy confirmed; **OR**
 - i. Diagnosis is confirmed by a fibrosis-4 index (FIB-4) score of more than 1.3 and less than 3.48 and ONE of the following:
 - a. Fibroscan score > 8 kPa
 - b. Enhanced liver fibrosis (ELF) score ≥ 9.8
 - c. Magnetic resonance elastography (MRE) score > 3.2 kPa; **AND**
 2. Documented liver fibrosis stage F2 or F3; **AND**
 3. Other causes of liver disease or hepatic steatosis have been ruled out (e.g., alcoholic steatohepatitis, acute fatty liver, autoimmune hepatitis, Hepatitis A, B or C, hemochromatosis, drug-induced liver disease, etc.); **AND**
 - D. Member has ONE of the following comorbidities:
 1. Overweight or Obesity (BMI ≥ 25 kg/m²)
 2. Hypertension
 3. Dyslipidemia
 4. Pre-diabetes

5. Type 2 Diabetes Mellitus; **AND**
 - E. Provider attestation member has adopted liver-protective lifestyle interventions such as optimizing weight loss, dietary changes, and exercise; **AND**
 - F. Provider attestation member is optimizing standard of care pharmacologic treatment to manage comorbid diseases, including, but not limited to cardiovascular disease, dyslipidemia, diabetes, hypertension; **AND**
 - G. Member does not have evidence of cirrhosis, hepatic decompensation, or hepatocellular carcinoma (HCC); **AND**
 - H. Treatment with semaglutide has been ineffective, contraindicated, or not tolerated
- II. Resmetirom (Rezdiffra) is considered investigational when used for all other conditions, including but not limited to:
 - A. Heterozygous Familial Hypercholesterolemia
 - B. Evidence of cirrhosis (F4), hepatic decompensation, or hepatocellular carcinoma (HCC)

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Disease response to treatment defined by improvement in fibrosis or stabilization/no worsening of fibrosis as determined by non-invasive tests (e.g., transient elastography (e.g., FibroScan), magnetic resonance elastography (MRE), etc.); **AND**
- IV. Member has not progressed to cirrhosis, experienced hepatic decompensation events, or hepatocellular carcinoma (HCC)

Supporting Evidence

- I. Resmetirom (Rezdiffra) is a liver-targeted thyroid hormone receptor-beta (THR- β) selective agonist for the treatment of adults with nonalcoholic steatohepatitis (NASH) with liver fibrosis. When activated in the liver, THR- β leads to the breakdown of stored fat.
- II. Non-alcoholic fatty liver disease (NAFLD) is characterized by an abnormal accumulation of fat in the liver. NAFLD can be subcategorized as nonalcoholic fatty liver (NAFL), in which there is hepatic steatosis (HS) but no injury to liver cells, and as nonalcoholic steatohepatitis (NASH), in which HS is accompanied by hepatocellular injury.
- III. NASH can progress to liver fibrosis, and liver fibrosis can progress to irreversible cirrhosis and hepatocellular carcinoma (HCC). NASH and alcoholism are the top two indications for liver transplantations and is the leading indication for liver transplantation in adults 65 years of age and older and women of all ages. NAFLD is closely linked to and often precedes the development of metabolic abnormalities (insulin resistance, dyslipidemia, obesity, and hypertension). Having several metabolic abnormalities confers an even greater risk of histological progression of NASH and all-cause mortality.

- IV. In 2023, it was proposed by hepatology medical societies that the naming for these conditions be updated to metabolic-associated fatty liver disease (MAFLD) and metabolic steatohepatitis (MASH).
- V. Diagnosis of suspected disease in most patients is based on clinical and laboratory data as well as imaging with appropriate exclusion of other liver conditions, but NASH is also a diagnosis of exclusion, which includes excluding: other causes of hepatic steatosis [alcoholic steatohepatitis, acute fatty liver, autoimmune hepatitis, Hepatitis A, B and C, hemochromatosis, drug-induced liver disease, etc.), absence of coexisting chronic liver disease, and exclusion of significant alcohol consumption.
- VI. Abnormal laboratory results indicating liver injury (e.g., aminotransferase levels (AST, ALT, etc.) may be detected and managed by primary care practitioners (PCPs), but should not be used in isolation to make a definitive NASH diagnosis. Individuals with intermediate to high-risk NASH or cirrhosis should be referred to hepatology or gastroenterology to undergo additional monitoring and confirmatory tests.
- VII. Liver biopsy is regarded as the gold standard to diagnose NASH. Several noninvasive testing (NIT) methods to detect fibrosis in patients with liver disease have been established as alternatives to biopsy, however may not provide accurate diagnostic specificity. Initial risk assessment begins with evaluation of risk of advanced fibrosis (fibrosis-4 index (FIB-4) tool). The FIB-4 tool is a blood-based calculation that estimates liver fibrosis. Those who may have a moderate or high risk of advanced disease based on FIB-4 (≥ 1.3 and < 3.48) should undergo secondary risk assessment such as transient elastography (TE) (e.g., Fibroscan), magnetic resonance elastography (MRE), and the enhanced liver fibrosis (ELF) test. A Fibroscan score of > 8 and MRE score > 3.2 kPa are suggestive of moderate to advanced fibrosis. The ELF test is used as prognostication and recommended as a secondary risk assessment, particularly when availability of elastography may be limited. An ELF score ≥ 9.8 indicates intermediate risk of fibrosis and disease progression to cirrhosis. Although standard ultrasound can detect hepatic steatosis, it is not recommended as a tool to identify hepatic steatosis due to low sensitivity across the NAFLD spectrum. Patients with advanced fibrosis require further assessment and additional MRI-based tools can be used to further risk stratify patients. When there is diagnostic uncertainty in patients with indeterminate, unreliable, or conflicting NITs, diagnosis via liver biopsy remains the most reliable method to confirm advanced fibrosis and progression of NASH.
- VIII. Metabolic dysfunction-associated steatotic liver disease (MASLD) is defined by presence of liver steatosis and one metabolic risk factor (e.g., obesity, diabetes mellitus, dyslipidemia, hypertension). Patients with hepatic steatosis or clinically suspected NAFLD based on the presence of obesity and metabolic risk factors should undergo primary risk assessment with a fibrosis risk stratification by the fibrosis-4 (FIB-4 index), which is a common noninvasive test to help estimate the amount of scarring in the liver. The score calculates age, AST and ALT levels, and platelet count.
- IX. The 2023 American Association for the Study of Liver Diseases (AASLD) and 2022 American Association of Clinical Endocrinology (AACE) guidelines provide guidance on the clinical care pathway for initial risk stratification and management of patients with NASH:
 - a. Low risk of advanced fibrosis is defined as an FIB-4 score < 1.3 , LSM < 8.0 kPa by transient elastography (TE) or a liver biopsy fibrosis stage of F0–F1.

- b. Intermediate/Indeterminate risk is defined as an FIB-4 score between ≥ 1.3 and 2.67 and/or an LSM between 8.0 and 12.0 kPa on TE, and in those patients who are unable or unwilling to obtain a liver biopsy.
 - c. High risk is defined as an FIB-4 score > 2.67 , LSM > 12.0 kPa by TE, or a liver biopsy that shows clinically significant liver fibrosis (F2–F4).
- X. There is no single or specific NIT that is recommended; however, liver-specific imaging, including vibration-controlled transient elastography (VCTE) (e.g., FibroScan®) are commonly used to assess liver stiffness and can be used to exclude significant hepatic fibrosis. VCTE can assess the presence of liver disease through a combination of controlled attenuation parameter (CAP) and liver stiffness measurement (LSM), which assess hepatic fat and liver stiffness, respectively. Changes in liver stiffness may be useful in identifying disease progression. Hepatic fat may also be assessed using magnetic resonance imaging-proton density fat fraction (MRI-PDFF), which determines fat content via the difference in resonance frequencies between fat and water and can additionally quantify steatosis. Other common NITs used in clinical practice include magnetic resonance elastography (MRE), enhanced liver fibrosis test (ELF), and acoustic radiation force impulse imaging (ARFI) (Virtual Touch™ tissue quantification, ElastPQ).
- XI. Patients with NASH and at least stage 2 fibrosis (F2), referred to as “at-risk” NASH, have a demonstrably higher risk of liver-related morbidity and mortality.
- XII. Lifestyle intervention is the key therapeutic intervention for patients with NAFLD. The American Association for the Study of Liver Diseases (AASLD) guidance on the management of NAFLD endorse dietary modification, increased physical activity, and weight loss. A weight loss of 5% to 10% of body weight can reverse hepatic steatosis and stabilize or diminish NASH in many patients, but this goal is frequently difficult to achieve. AASLD emphasizes optimizing glucose control for patients with diabetes, lipid-lowering therapy for patients with hyperlipidemia, and abstinence from alcohol for patients with clinically significant hepatic fibrosis.
- XIII. Goal of pharmacologic therapy for NASH is to slow the progress of, halt, or reverse fibrosis while patients are still pre-cirrhotic. As of December 2023, resmetirom (Rezdiffra) is anticipated to be the first FDA-approved therapy for NASH. Vitamin E and pioglitazone have been used historically and may improve the histologic changes of NASH, but data are limited. Some of the medications approved for commonly associated comorbidities such as T2DM and obesity have been studied in the context of NASH and may reduce liver enzymes or steatosis or improve liver histology. Therefore, medications with possible liver-related benefits should be optimized when managing comorbidities.
- XIV. MAESTRO-NASH is an ongoing randomized, double-blind, placebo-controlled Phase 3 trial in patients with NASH and liver fibrosis. This study incorporates a 52-week serial liver biopsy analysis in 966 patients with biopsy-confirmed NASH and significant fibrosis (stage F1b, F2, F3). Patients were randomly assigned to placebo, resmetirom 80 mg, or resmetirom 100 mg once daily. Baseline characteristics were balanced across treatment arms and include BMI 36 kg/m², type 2 diabetes (67%), hypertension (78%), dyslipidemia (71%; LDL 99 mg/dL); baseline liver biopsy nonalcoholic fatty liver disease activity score (NAS) ≥ 5 (84%); baseline fibrosis stage: F3 (62%), F2 (33%), F1B (5%). The NAS is a validated scoring system with

- scores ranging from 0–8 and are composed of the unweighted sum of semi-quantitative steatosis (0–3), ballooning (0–2), and lobular inflammation scores (0–3).
- XV. Dual primary endpoints evaluated the proportion of patients with NASH resolution with at least 2 points reduction in without worsening of fibrosis at least 1 point improvement in the fibrosis stage with no worsening of NAS. Key secondary endpoint included percent change from baseline in LDL-C (after 24 weeks). The 52-week dual primary endpoint and the key secondary endpoint were met for both the 80 mg and 100 mg dose of resmetirom (Rezdiffra). 26% (80 mg) and 30% (100 mg) of patients randomized to resmetirom had NASH resolution without worsening of fibrosis stage compared to 10% of the placebo group ($p < 0.0001$ for both comparisons). Additionally, 24% (80 mg) and 26% (100 mg) of patients randomized to resmetirom had ≥ 1 stage improvement in fibrosis without worsening of NASH compared with 14% for the placebo group ($p < 0.0001$ for both comparisons).
 - XVI. The onset of adverse events (AEs) were typically observed during the first weeks of treatment, and most treatment-related AEs were considered mild or moderate in severity, and transient. The overall incidence of AE was comparable between treatment groups, with most common AE ($>10\%$) in resmetirom arm being diarrhea, nausea, vomiting, arthralgia, urinary tract infection, and COVID-19 infection. There were no instances of drug induced liver injury (DILI).
 - XVII. Framework recommendations are based on critical appraisal of the evidence for safety and efficacy and defines clinically meaningful endpoints/benefits inclusive of, but are not limited to morbidity, mortality, symptom control, physical/emotional functioning, and quality of life. Historically, several pharmacologic therapies have been studied for the treatment of patients with NASH, however, most trials have not been able to detect a clinically meaningful difference, had significant safety issues, and/or been too short to determine an impact on important patient-centered clinical outcomes. The quality of evidence is considered moderate, as resmetirom (Rezdiffra) met both dual primary endpoints and achieved greater rates of stabilization of fibrosis compared to placebo. Fibrosis histology is an accepted surrogate endpoint and one of the strongest predictors for clinical outcomes; however, uncertainty remains regarding the magnitude of the long-term benefits of resmetirom (Rezdiffra). The effects of resmetirom (Rezdiffra) on the ultimate progression of NASH to worsening fibrosis, cirrhosis, and the outcomes of liver failure, need for transplantation, and early mortality cannot be known from this relatively short-term pivotal trial.
 - XVIII. Data from the MAESTRO-NASH trial will be reinforced by the Phase 3 MAESTRO clinical development program, including the MAESTRO-NASH-OUTCOMES, MAESTRO-NAFLD-1 and MAESTRO-NAFLD-OLE safety clinical trials. Resmetirom (Rezdiffra) was approved under the accelerated approval pathway based on evaluating liver histological improvements predicted to slow the progression of NASH defined as resolution of NASH without worsening fibrosis stage or improvement in fibrosis stage with no worsening of NAS. Continued approval for the treatment of NASH is contingent upon verification and description of clinical benefit in confirmatory trials. The 54-month analysis of MAESTRO-NASH in approximately 1,700 patients is on-going and will include the following endpoints: a composite clinical outcome composed of all-cause mortality, liver transplant, and significant hepatic events (including hepatic decompensation events [ascites, encephalopathy, or

- variceal hemorrhage], histological progression to cirrhosis, and a confirmed increase of MELD score.
- XIX. Guidelines recommend resmetirom (Rezdiffra) in treatment of non-cirrhotic MASH (strong recommendation, consensus). Guidelines have not been updated to include semaglutide. There are no head-to-head trials comparing efficacy and safety of resmetirom (Rezdiffra) to semaglutide and superiority/inferiority cannot be concluded. Semaglutide recently demonstrated statistically significant resolution of steatohepatitis with no worsening of liver fibrosis compared to placebo (62.9% vs 34.1%, difference 28.9% ($P < 0.0001$)) and improvements in fibrosis with no worsening of steatohepatitis compared to placebo (37.0% vs 22.5%, difference 14.5%, $P < 0.0001$) in the ESSENCE trial. Semaglutide demonstrated a similar effect in resolution of fibrosis and steatohepatitis in patients with NASH/MASH compared to resmetirom (Rezdiffra). In the MAESTRO-NASH, prior use of GLP1 agonists was permitted. Therefore, requiring step through semaglutide for NASH/MASH is both clinically appropriate and cost-effective.

Investigational or Not Medically Necessary Uses

- I. Resmetirom (Rezdiffra) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
- A. Heterozygous Familial Hypercholesterolemia (HeFH)
 - i. Resmetirom (Rezdiffra) was evaluated in a 12-week, double-blind, randomized, placebo-controlled Phase 2 trial in patients with HeFH (NCT03038022). Resmetirom reduced LDL-C levels by 18.8% (95% CI: -27.8% to -9.8%; $P < 0.0001$) compared with placebo at Week 12, with a mean difference of -27 mg/dL (95% CI: -38.4 to -15.5 mg/dL; $P < 0.0001$). Study limitations included small sample size, short treatment and follow-up duration, and inclusion of a homogeneous population. Additional studies are needed to further evaluate the potential role of resmetirom in the management of patients with HeFH.
 - B. Cirrhosis, hepatic decompensation, or hepatocellular carcinoma (HCC)
 - i. Patients with cirrhosis, patients with prior hepatic decompensation events (e.g., variceal hemorrhage, ascites, hepatic encephalopathy), or in hepatocellular carcinoma (HCC) were excluded from participating in the MAESTRO-NASH clinical program. Reversal of cirrhosis in these patients may not be feasible and the efficacy and safety of resmetirom in this patient population is unknown.

References

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[information/search-fda-guidance-documents/noncirrhotic-nonalcoholic-steatohepatitis-liver-fibrosis-developing-drugs-treatment](#)

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
obeticholic acid (Ocaliva)	Primary Biliary Cholangitis (PBC)
semaglutide (Wegovy)	Major adverse cardiovascular events (MACE) risk
	Excess body weight and weight maintenance in patients 12 years and older with obesity and adults with overweight
	Nonalcoholic steatohepatitis (NASH)/ Metabolic Dysfunction-Associated Steatohepatitis (MASH)

Policy Implementation/Update

Action and Summary of Changes	Date
Updated MASH criteria to include non-invasive testing and one comorbid condition. Updated relevant supporting evidence	10/2025
Live 08/18/2025: Updated criteria to require step through semaglutide and added supporting evidence	05/2025
Policy created	02/2024

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP324

Split Fill Management*

Description

Revumenib (Revuforj) is an orally administered menin inhibitor for the treatment of relapsed or refractory acute leukemia with a lysine methyltransferase 2A (KMT2A) gene translocation.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
revumenib (Revuforj)	Acute myeloid leukemia, relapsed/refractory	25 mg tablets	60 capsules/30 days
		110 mg tablets	
	Acute lymphoblastic leukemia, relapsed/refractory	160 mg tablets	

Initial Evaluation

- I. **Revumenib (Revuforj)** may be considered medically necessary when the following criteria are met:
 - A. Member is one year of age or older; **AND**
 - B. A documented height and weight or BSA within the last 3 months; **AND**
 - C. Medication is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
 - D. Medication will not be used in combination with any other oncology therapy; **AND**
 - E. Attestation that the member does not qualify for any actively enrolling clinical trials for the treatment of AML or ALL; **AND**
 - F. A diagnosis of **relapsed or refractory acute leukemia [i.e., acute myeloid leukemia (AML) or acute lymphocytic leukemia (ALL)]** when all the following are met:
 1. Presence of KMT2A mutation status as detected by an FDA-approved test; **AND**
 2. Treatment with one of the following has been ineffective, or not tolerated unless both are contraindicated:
 - i. Systemic chemotherapy; **OR**
 - ii. Allogenic hematopoietic stem cell transplant; **AND**
 3. Provider attestation that all standard therapies have been exhausted.
- II. Revumenib (Revuforj) is considered investigational when used for all other conditions, including but not limited to:
 - A. Revumenib (Revuforj) used in combination with another oncology therapy
 - B. Newly diagnosed acute leukemia

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- C. Acute leukemia in the absence of KMT2A mutation
- D. Acute leukemia with an NPM1 mutation

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Medication will not be used in combination with any other oncology therapy; **AND**
- IV. Member has exhibited improvement or stability of disease symptoms [e.g., no signs of unacceptable toxicity or intolerance, no signs of disease progression, become independent of red blood cell and platelet transfusion]

Supporting Evidence

- I. Given the complexities involved with the diagnosis and management of acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL), treatment with revumenib (Revuforj) must be initiated and/or supervised by an oncologist or hematologist. Choice of initial and later-line therapies in the setting of relapsed/refractory (R/R) AML and ALL are contingent upon patient specific characteristics, disease-risk, and cytogenetic stratification.
- II. Revumenib (Revuforj) is a menin inhibitor that was studied in an open-label, single-arm, multicenter Phase I/II trial of 135 participants with relapsed/refractory AML or ALL with a confirmed KMT2A gene rearrangement mutation (AUGMENT-101). Participants included children and adults with a median age of 35 years, female (64%), highly refractory relapsed patients who had at least one relapse with no response to their most recent salvage therapy (59%). For inclusion participants must have tried at least one previous line of therapy. Participants received a twice daily dose of revumenib (Revuforj) and the efficacy measure was the rate of complete remission (CR) or CR with partial hematological recovery (CRh), duration of CR+CRh, and the conversion from transfusion dependence to independence. The efficacy analysis included 104 participants and 21.2% achieved CR+CRh, a median duration of response of 6.4 months, and 14% of transfusion dependent participants became independent while 48% of independent participants remained transfusion independent.
- III. Common adverse reactions include hemorrhage (53%), nausea (51%), musculoskeletal pain (42%), infection (41%), and febrile neutropenia (35%) on revumenib (Revuforj) treatment. Serious adverse reactions were reported in 73% of participants which included infection (24%), febrile neutropenia (19%), bacterial infection (17%), differentiation syndrome (12%), hemorrhage (9%), and thrombosis (5%).
- IV. There were 14 documented deaths at the interim analysis cutoff during the Phase II review, in which five individual participants who experienced an intracranial hemorrhage, myocardial ischemia, pneumonia, and respiratory failure were deemed to be possibly related to revumenib (Revuforj).
- V. National Comprehensive Cancer Network (NCCN) guidelines for the treatment of AML were updated in January 2025 to recommend revumenib (Revuforj) as monotherapy for relapsed/refractory disease with KMT2A mutation as category 2A recommendation. This is then

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suggested to be followed by hematopoietic stem cell transplantation (HSCT). Other therapies include intensive and less intensive chemotherapy regimens based on patient-specific factors and tolerability, which most are listed as a 2A recommendation except for CLIA + venetoclax and LDAC, which are category 2B.

- VI. National Comprehensive Cancer Network (NCCN) guidelines for the treatment of ALL were updated in December 2024 to recommend revumenib (Revuforj) as monotherapy for relapsed/refractory disease with a KMT2A mutation as a category 2A recommendation. This recommendation is for disease with Philadelphia (Ph) positive - B-ALL and T-ALL; the recommendation is not included in Ph+ B-ALL disease. Other treatments for Ph- B-ALL include blinatumomab (Blinicyto) and inotuzumab (Besponsa), which are listed as a category 1 recommendation. Additional therapies in this space also include CAR T-cell therapies. Other treatments for T-ALL prefer nelarabine with or without etoposide and cyclosporine, along with other chemotherapy combinations including venetoclax, bortezomib, cytarabine or fludarabine-containing regimens.

Investigational or Not Medically Necessary Uses

- I. Revumenib (Revuforj) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
- A. Use in combination therapy with other oncolytic agents
 - i. Current clinical trial data leading to FDA approval is in the monotherapy setting. Safety and efficacy has not been established for combination regimens.
 - B. Treatment of newly diagnosed acute leukemia
 - i. There is no published data to support use of revumenib (Revuforj) in newly diagnosed patients.
 - ii. Clinical trials are being conducted in patients with newly diagnosed AML. There is currently insufficient evidence to support the safety and efficacy of revumenib (Revuforj) for the treatment of newly diagnosed disease.
 - C. Treatment of acute leukemia without a known KMT2Ar mutation
 - i. There is lack of evidence to suggest the use of revumenib (Revuforj) in patients with acute leukemia without a KMT2Ar mutation. Patients who did not have confirmed mutation status were excluded from the trials.
 - D. Treatment of acute leukemia with an NPM1 mutation
 - i. This is part of the ongoing phase 2C of the AUGMENT-101 trial for use in relapsed/refractory AML with an NPM1 mutation. As of March 2025, data to support use in this population has not been published.

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy

Policy Name	Disease state
venetoclax (Venclexta®)	Newly diagnosed acute myeloid leukemia (AML)
azacitidine (Onureg®)	Acute Myeloid Leukemia (AML), maintenance treatment after first complete remission
glasdegib (DAURISMO®)	Newly diagnosed acute myeloid leukemia (AML)
midostaurin (Rydapt®)	Acute myeloid leukemia, newly diagnosed, FLT3 mutation-positive, in combination with cytarabine/daunorubicin induction and cytarabine consolidation
dasatinib (SPRYCEL®)	Philadelphia chromosome-positive (Ph+) acute myeloid leukemia (ALL)
ponatinib (Iclusig®)	Newly diagnosed Ph+ ALL in combination with chemotherapy
IDH Inhibitors	Acute myeloid leukemia, relapsed/refractory; Acutely myeloid leukemia, newly diagnosed
gilteritinib (XOSPATA®)	Relapsed/refractory FLT3-mutated acute myeloid leukemia (AML)
imatinib (Gleevec®)	Philadelphia chromosome-positive acute lymphoblastic leukemia, newly diagnosed, in combination with chemotherapy Philadelphia chromosome-positive acute lymphoblastic leukemia, relapsed/refractory

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2025

Policy Type: PA

Pharmacy Coverage Policy: UMP056

Description

Rifaximin (Xifaxan) is an orally administered rifamycin antibacterial agent that inhibits bacterial RNA synthesis by binding to bacterial DNA-dependent RNA polymerase.

Length of Authorization

- Initial:
 - i. Irritable Bowel Syndrome with Diarrhea (IBS-D): one time approval
 - ii. Hepatic encephalopathy: six months
 - iii. Traveler's diarrhea: one time approval
- Renewal:
 - i. IBS-D: one-time approval, maximum of three fills per lifetime
 - ii. Hepatic encephalopathy: 12 months
 - iii. Traveler's diarrhea: N/A

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit	DDID
rifaximin (Xifaxan)	550 mg tablets	Treatment of irritable bowel syndrome with diarrhea (IBS-D).	42 tablets/ 14 days	150969, 152498
		Hepatic encephalopathy recurrence.	60 tablets/30 days	
	200 mg tablets	Travelers' diarrhea caused by noninvasive strains of Escherichia coli	9 tablets/3 days	088395, 088393

Initial Evaluation

- I. Rifaximin (Xifaxan) may be considered medically necessary when the following criteria below are met:
 - A. A diagnosis of one of the following:
 - i. **Irritable Bowel Syndrome with Diarrhea (IBS-D); AND**
 - a. Member is 18 year of age or older; **AND**
 - b. Rifaximin (Xifaxan) is prescribed by or in consultation with a gastroenterologist; **AND**
 - c. Treatment with at least three therapies from different groups have been tried and failed, not tolerated or all are contraindicated (please note, if one or more groups is contraindicated, a trial of three agents from the remaining classes will be required):
 - a. Group 1: antidiarrheal (e.g., loperamide, bismuth subsalicylate, diphenoxylate/atropine, paregoric)
 - b. Group 2: bile acid sequestrant (e.g., cholestyramine, colestipol)
 - c. Group 3: antispasmodic (e.g., dicyclomine, hyoscyamine)

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- d. Group 4: Tricyclic serotonergic agent: (e.g., amitriptyline, nortriptyline, imipramine, desipramine)

OR

ii. **Traveler's diarrhea; AND**

- a. Member is 12 years of age or older; **AND**
- b. Treatment with azithromycin (Zithromax) or a fluoroquinolone (e.g., ciprofloxacin) have been ineffective, not tolerated, or BOTH are contraindicated; **OR**

iii. **Hepatic encephalopathy; AND**

- a. Member is 18 year of age or older; **AND (a or b)**
 - a. Treatment with lactulose has been ineffective, contraindicated, or not tolerated; **OR**
 - b. Rifaximin (Xifaxan) will be used as add-on treatment

II. Rifaximin (Xifaxan) is considered investigational when used for all other conditions, including but not limited to:

- A. Small Intestinal Bacterial Overgrowth (SIBO)

Renewal Evaluation

I. **Irritable Bowel Syndrome with Diarrhea (IBS-D); AND**

- A. There has been a 10 week treatment-free period since prior approval of rifaximin (Xifaxan); **AND**
- B. The member has not had more than two prior treatments with rifaximin (Xifaxan). A maximum of three approvals is allowed per lifetime for the treatment of IBS-D; **OR**

II. **Hepatic encephalopathy; AND**

- A. Clinical documentation indicating disease stability or improvement.

Supporting Evidence

- I. Rifaximin (Xifaxan) is indicated for adults and pediatric patients 12 years of age and older with travelers' diarrhea, and adults older than 18 years of age with hepatic encephalopathy or IBS-D. Infectious Diseases Society of America clinical practice guidelines recommend treatment with fluoroquinolones or azithromycin as first line treatment of travelers' diarrhea.
- II. The FDA approved dose is 200 mg three times daily for three days for traveler's diarrhea.
- III. The American Association for the Study of Liver Diseases and European Association for the Study of the Liver clinical practice guidelines suggest initial therapy with lactulose for the treatment of hepatic encephalopathy. Rifaximin (Xifaxan) is an effective add-on therapy to lactulose for prevention of recurrence.
- IV. Treatment options for IBS-D include antidiarrheals, antibiotics, antispasmodics, antidepressants, and bile acid sequestrants. The American College of Gastroenterology gave moderate or weak recommendations for all IBS-D therapies due to poor quality of evidence and applicability to patient groups. Due to insufficient comparative evidence for efficacy, other treatment options provide a better value over rifaximin (Xifaxan). Of the antidepressants, tricyclic agents have

shown to slow intestinal transit; however, SSRI/SNRI agents have less published data and the data available is inconsistent in showing benefit in IBS.

- V. Rifaximin (Xifaxan) will be authorized for a total of three courses per lifetime for IBS-D per FDA label. In clinical studies, 14-day repeat treatment courses were separated by 10 weeks.

Investigational or Not Medically Necessary Uses

I. Small Intestinal Bacterial Overgrowth (SIBO)

- A. Although likely an association exists between IBS-D and SIBO, the evidence linking a causal relationship between the two diagnoses is conflicting.
- B. Intestinal motility disorders and chronic pancreatitis are estimated to account for approximately 90 percent of cases of SIBO. Underlying etiology of SIBO should be addressed prior to pharmacologic therapy. Common causes of SIBO include: anatomic abnormalities; strictures, motility issues, hypochlorhydria, immunodeficiency, chronic pancreatitis, cirrhosis, end stage renal disease, or medications (e.g., proton pump inhibitors, tricyclic antidepressants, opioids).
- C. Rifaximin (Xifaxan) use in adults with SIBO has not been evaluated in multicenter, prospective, randomized, placebo-controlled trials. Although five single-site, open-label, randomized controlled trials demonstrated a potential modest benefit of rifaximin (Xifaxan) use in adults with a SIBO, the studies were poorly designed, had a small sample size, and had minimal follow up.
- D. Gastroenterological Association Institute clinical guidelines for treatment of SIBO have not been established.

References

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Policy Implementation/Update:

Date Created	August 2015
Date Effective	August 2015
Last Updated	July 2019
Last Reviewed	08/2015; 04/2019, 07/2019

Action and Summary of Changes	Date
Criteria for the IBS-d indicated updated to require three prior therapies prior to payment consideration. Additionally, agents with low quality or conflicting data were removed from the list of conventional agents allowed for previous trial and failure. Rearrangement of criteria to include the most requested indication first.	07/2019
Updated to policy format, evidence for the investigational use of rifaximin (Xifaxan) in SIBO updated, addition of specialist involvement in prescribing for IBS-D, age criteria edited.	04/2019

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP214

Description

Riluzole (Rilutek®, Teglutik®, Exervan®) is an orally administered benzothiazole for the treatment of patients with amyotrophic lateral sclerosis (ALS).

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
riluzole (Rilutek) *	50 mg tablet	Amyotrophic lateral sclerosis (ALS)	60 tablets/30 days
riluzole (Teglutik)	50 mg/10 mL (5 mg/mL) oral suspension		600 ml/30 days
riluzole (Exervan)	50 mg film		60 films/30 days

*Generic riluzole is a formulary agent and does not require prior authorization

Initial Evaluation

- I. Riluzole (Rilutek, Teglutik, Exervan) may be considered medically necessary when the following criteria are met:
 - A. Member is 18 years of age or older; **AND**
 - B. Medication is prescribed by, or in consultation with, a neurologist; **AND**
 - C. A diagnosis of **Amyotrophic lateral sclerosis (ALS)**; **AND**
 - D. Treatment with generic riluzole tablet has been ineffective, contraindicated, or not tolerated.
- II. Riluzole (Rilutek, Teglutik, Exervan) are considered investigational when used for all other conditions, including but not limited to:
 - A. Treatment-resistant depression
 - B. Chorea in Huntington's disease

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise.; **AND**

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- III. Documentation of clinical benefit, including stabilization of disease and absence of unacceptable toxicity from the drug [e.g. hepatic injury, severe neutropenia, interstitial lung disease]; **AND**
- IV. Treatment with generic riluzole tablet has been ineffective, contraindicated, or not tolerated

Supporting Evidence

- I. According to the American Academy of Neurology (AAN) two randomized controlled clinical trials and one cross-sectional study, show that multidisciplinary clinics specializing in ALS care are likely effective in several ways, which include improved quality of life and lengthened survival. The AAN guidelines recommend that specialized multidisciplinary clinical referral should be considered for patients with ALS to optimize health care delivery and prolong survival and may be linked to enhanced quality of life.
- II. The safety and efficacy of riluzole (Rilutek®) in pediatric patients with amyotrophic lateral sclerosis (ALS) has not been established.
- III. According to the American Academy of Neurology (AAN) practice parameter for the care of patients with ALS, riluzole is safe and effective for slowing disease progression to a modest degree in ALS. They therefore recommend that riluzole should be offered to slow disease progression in patients with ALS.

Investigational or Not Medically Necessary Uses

- I. In a randomized, double-blind, placebo-controlled sequential trial that evaluated the efficacy and safety of adjunctive riluzole for treatment-resistant major depressive disorder (MDD), 104 participants were randomized in a 2:3:3 ratio to receive riluzole/riluzole, placebo/placebo and placebo/riluzole. The trial had two phases of 4 weeks each, and the primary endpoint was change in depression severity as assessed by the Montgomery-Åsberg Depression Rating Scale (MADRS), which did not show a statistically significant difference between riluzole and placebo.
- II. Chorea is a hallmark of Huntington Disease (HD), along with cognitive decline and psychiatric impairment. The AAN guidelines for pharmacologic treatment of HD, notes two randomized controlled trials evaluating riluzole for chorea for HD using different doses (100 mg or 200 mg) and durations (8 weeks and 3 years). The first study (n=63) showed a statistically significant reduction in unified huntington's disease rating scale (UHDRS) in patients who received riluzole 200 mg/day (-2.2 ± 3.3 , $p 0.01$); however, statistical significance was observed in those who received riluzole 100 mg/day [-0.2 ± 2.9 ; vs placebo ($\pm 0.7 \pm 3.4$)]. In the second study (n=537), no statistically significant difference in UHDRS chorea scores at 3 years was observed between participants who received riluzole 50 mg twice daily and placebo. Although the guidelines recommend riluzole 200 mg/day with level B of evidence for HD chorea, there is modest evidence on the efficacy and safety of riluzole for chorea in HD.

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Policy Implementation/Update:

Action and Summary of Changes	Date
Added Exervan to policy	09/2021
Criteria changed to policy format, added age requirement, specialist referral/prescription, step through generic riluzole tablet and renewal evaluation.	12/2020
Criteria created	07/2013

Policy Type: PA

Pharmacy Coverage Policy: UMP207

Description

Ripretinib (Qinlock) is an orally administered tyrosine kinase inhibitor (TKI) that inhibits KIT proto-oncogene receptor tyrosine kinase (KIT) and platelet derived growth factor receptor A (PDGFRA) kinase.

Length of Authorization

- I. Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
riporetinib (Qinlock)	50 mg tablets	Gastrointestinal Stromal Tumor, advanced disease after treatment with three or more tyrosine kinase inhibitors, including imatinib	90 tablets/30 days

Initial Evaluation

- I. Ripretinib (Qinlock) may be considered medically necessary when the following criteria are met:
 - A. Member is 18 years of age or older; **AND**
 - B. Medication is prescribed by, or in consultation with, an oncologist; **AND**
 - C. Ripretinib (Qinlock) will be used as monotherapy (i.e., will not be used in combination with any other oncology therapy); **AND**
 - D. A diagnosis of **Gastrointestinal Stromal Tumor (GIST)** when the following are met:
 - 1. Member has advanced (Stage III), unresectable or metastatic (Stage IV) disease; **AND**
 - 2. Member has previously progressed on, or after, **ALL** of the following:
 - a. imatinib (e.g., Gleevec)
 - b. sunitinib (Sutent)
 - c. regorafenib (Stivarga)
- II. Ripretinib (Qinlock) is considered investigational when used for all other conditions, including but not limited to:
 - A. Third-line or prior treatment of gastrointestinal stromal tumor
 - B. Advanced Systemic Mastocytosis or other hematologic malignancies
 - C. Soft Tissue Sarcoma, outside of gastrointestinal stromal tumor
 - D. Malignant Gliomas
 - E. Melanoma
 - F. Germ Cell, Penile Cancer

- G. Non-Small Cell Lung Carcinoma (NSCLC)
- H. Other Advanced Solid Tumor Cancers/Malignancies

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Ripretinib (Qinlock) will be used as monotherapy (i.e., will not be used in combination with other oncologic medications); **AND**
- IV. Member has experienced response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread

Supporting Evidence

- I. Ripretinib (Qinlock) was evaluated in INVICTUS - a randomized (2:1), double-blind, placebo-controlled study in adults with advanced gastrointestinal stromal tumors. The trial included 129 subjects who had previously progressed on or after imatinib, sunitinib, and regorafenib, or had documented intolerance to any of these treatments despite dose modifications. Mutation status was collected but was not utilized as part of the inclusion criteria for this trial. Ripretinib (Qinlock) was evaluated as monotherapy, and use of ripretinib (Qinlock) in addition to other oncologic therapies has not been evaluated for safety and/or efficacy.
- II. The primary efficacy endpoint was progression-free survival (PFS) and notable secondary endpoints included objective response rate (ORR), overall survival (OS), and quality of life (QOL). Ripretinib (Qinlock) showed statistically significant results in PFS compared to placebo [6.3 months vs. 1.0 months; HR 0.15; 95% CI 0.09-0.25; p<0.001]; however, there was not a statistically significant difference in ORR. Due to a hierarchical testing procedure of endpoints, overall survival and quality of life could not be formally tested for statistical significance given the insignificance of the ORR result.
- III. The safety profile of ripretinib (Qinlock) is similar to that of other TKIs. The most common treatment-related treatment emergent adverse events (occurring in 20% or more of patients in the ripretinib group) during the INVICTUS trial included alopecia, myalgia, nausea, fatigue, palmar-plantar erythrodysesthesia (also known as hand-foot syndrome), and diarrhea. There are no contraindications to ripretinib (Qinlock); however, warnings and precautions include: palmar-plantar erythrodysesthesia syndrome, new primary cutaneous malignancies, hypertension, cardiac dysfunction, risk of impaired wound healing, and embryo-fetal toxicity. Ripretinib (Qinlock) was studied in adult patients age 18 and older and has not been evaluated for safety and/or efficacy in pediatric patients. FDA-approval has only been granted for adult patients.
- IV. Gastrointestinal Stromal Tumor (GIST) is a rare subtype of soft tissue sarcoma, thus a definitive diagnosis from a specialty provider is warranted.

- V. NCCN Guidelines recommend ripretinib (Qinlock) as fourth-line therapy for the treatment of unresectable or metastatic GIST for those who have progressed after imatinib (Gleevec), sunitinib (Sutent), and regorafenib (Stivarga) with a Category 2A recommendation.

Investigational or Not Medically Necessary Uses

- I. Ripretinib (Qinlock) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
- A. Third-line or prior treatment for Gastrointestinal Stromal Tumor
 - B. Advanced Systemic Mastocytosis or other hematologic malignancies
 - C. Soft Tissue Sarcoma
 - D. Malignant Gliomas
 - E. Melanoma
 - F. Germ Cell, Penile Cancer
 - G. Non-Small Cell Lung Carcinoma (NSCLC)
 - H. Other Advanced Solid Tumor Cancers/Malignancies

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Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	11/2020

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP208

Description

Risdiplam (Evrysdi) is an orally administered survival of motor neuron 2 (SMN2) splicing modifier.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
risdiplam (Evrysdi)	Spinal Muscular Atrophy	60 mg/80 mL (0.75 mg/mL) solution	240 mL/30 days
		5 mg tablets	30 tablets/30 days

Initial Evaluation

- I. **Risdiplam (Evrysdi)** may be considered medically necessary when the following criteria are met:
 - A. Medication is prescribed by, or in consultation with, a neuromuscular specialist; **AND**
 - B. Provider attestation that nusinersen (Spinraza) will not be used concurrently with risdiplam (Evrysdi); **AND**
 - C. A diagnosis of **5q spinal muscular atrophy (SMA)** when the following are met:
 1. Homozygous deletion of the *SMN1* gene or dysfunctional mutation of the *SMN1* gene; **AND**
 2. Provider attests member does not require invasive ventilation or tracheostomy; **AND**
 3. Provider attestation the member has not had treatment with onasemnogene abeparvovec-xioi (Zolgensma); **AND**
 4. Member must have ONE of the following SMA phenotypes:
 - i. Pre-symptomatic SMA with two or three copies of the *SMN2* gene; **OR**
 - ii. SMA Type I; **OR**
 - iii. SMA II with symptomatic disease (e.g., impaired motor function and/or delayed motor milestones); **OR**
 - iv. SMA III with symptomatic disease (e.g., impaired motor function and/or delayed motor milestones); **AND**
 5. Baseline documentation of at least ONE of the following motor function/milestone measures:
 - i. Members less than two years of age:
 - a. Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND), OR Hammersmith Infant Neurologic Exam (HINE); **OR**
 - ii. Members two years of age or older:

- a. Motor Function Measure 32 (MFM32), Revised Upper Limb Module (RULM), Hammersmith Functional Motor Scale Expanded (HFMSE), OR Six-Minute Walk Test (6MWT).
- II. Risdiplam (Evrysdi) is considered investigational when used for all other conditions, including but not limited to:
 - A. Use in members with Type IV SMA
 - B. Use in combination with nusinersen (Spinraza)
 - C. Use after treatment with onasemnogene abeparvovec-xioi (Zolgensma)

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Member has responded to therapy, defined as stability or improvement in net motor function/milestones, compared to pretreatment baseline as exemplified by at least ONE of the following:
 - A. Members less than two years of age:
 1. Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND), Hammersmith Infant Neurologic Exam (HINE), OR Bayley Scales of Infant Development—Third Edition (BSID-III) Item 22; **OR**
 - B. Members two years of age or older:
 1. Motor Function Measure 32 (MFM32), Revised Upper Limb Module (RULM), Hammersmith Functional Motor Scale Expanded (HFMSE), OR Six-Minute Walk Test (6MWT); **OR**
 - C. Provider attests that member has had a slowed rate of decline in the aforementioned measures compared to pretreatment rate.

Supporting Evidence

- I. Spinal Muscular atrophy (SMA) is an autosomal recessive genetic disorder caused by mutations in chromosome 5q that lead to survival motor neuron (*SMN*) protein deficiencies. *SMN* protein from the *SMN1* gene, located on chromosome 5, is expressed in all cells and is required for life. In order to develop SMA, an individual must inherit two faulty *SMN1* genes, one from each parent; however, the majority of mutations responsible for 5q-SMA are either deletions or gene conversions.
- II. SMA subtype/phenotype is determined primarily by motor milestone attained. Risdiplam (Evrysdi) is FDA approved to treat pediatric and adult patients with pre-symptomatic or symptomatic SMA. Pre-symptomatic patients do not present with symptoms of SMA but have been genetically diagnosed in utero or via newborn screening. SMA trials have shown that patients who begin treatment earlier may have more favorable outcomes.
- III. Risdiplam (Evrysdi) is being evaluated in two ongoing Phase 2/3 trials (FIREFISH, SUNFISH) and an ongoing, phase 2 trial (RAINBOWFISH). FIREFISH is evaluating patients with infantile-onset

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Type I SMA and SUNFISH is evaluating patients with later-onset Type II and non-ambulatory Type III. RAINBOWFISH is enrolling pre-symptomatic infants two months of age or younger with SMA. All three studies require a confirmed diagnosis of 5q-autosomal recessive SMA prior to enrollment. Patients requiring invasive ventilation or tracheostomy are excluded from all three clinical trials (FIREFISH, SUNFISH, RAINBOWFISH); therefore, there are no data to show efficacy and safety in this patient population.

- IV. FIREFISH is an open-label, two-part study designed to assess safety, tolerability, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD). The study included 21 patients in Part One and 41 patients in Part Two aged one to seven months with Type I SMA. The following endpoints were used: Bayley Scales of Infant Development–Third Edition (BSID-III) Item 22, Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND), and Hammersmith Infant Neurologic Exam (HINE).
 - BSID-III is a clinical evaluation developed to help identify children with developmental delay who may require intervention services. The BSID-III consists of three areas of development: cognitive, language, and motor. Effectiveness was established based on the ability to sit without support for at least five seconds (as measured by Item 22). This scale is intended for pediatrics only and is not specific to SMA.
 - CHOP-INTEND is a validated, 16-item, 64-point scale, designed to measure motor function for weak infants with Type I SMA and is intended for pediatrics only. It measures spontaneous upper and lower extremity movement, hand grip, head in midline with visual stimulation, hip adductors, rolling from legs and arms, shoulder and elbow flexion by itself and in addition to horizontal abduction, knee extension, hip flexion and foot dorsiflexion, head control, head/neck extension, and spinal incurvation. Each of the 16 items is graded on a scale of zero to four, with zero meaning no response and four meaning complete response.
 - HINE-2 is an SMA-specific measurement, 8-item, 26-point scale, designed to measure motor skills in infants with SMA. A score of zero for items such as sitting, crawling, and walking is expected for Type I. It measures voluntary grasp, ability to kick, head control, rolling, sitting, crawling, standing, and walking.
 - The primary efficacy outcome in FIREFISH Part One was dose determination for Part Two of the study, which was 0.2 mg/kg/day. The primary efficacy outcome in FIREFISH Part Two was the proportion of infants sitting without support for at least five seconds as assessed by the Gross Motor Scale of the BSID-III at Month 12, which was 29% (90% CI: 17.8 to 43.1%). Key secondary efficacy outcomes in FIREFISH Part One include BSID-III at Month 12, which was 33%; infants alive with no permanent ventilation, 90.5%; proportion of infants who require hospitalization, and 38% did not require hospitalization. Key secondary efficacy outcomes in FIREFISH Part Two include HINE-2, which was 78% (p<0.0001) while the proportion of patients who achieved at least four points on the CHOP-INTEND score was 90% (p<0.0001).
- V. SUNFISH is a two-part randomized, placebo-controlled study designed to assess safety, tolerability, efficacy, PK, and PD. The study included 51 patients in Part One and 180 patients in Part Two aged two to 25 with Type II or III SMA. Patients in Part Two of SUNFISH were randomized. The following endpoints were used: Motor Function Measure 32 (MFM-32) and Revised Upper Limb Module (RULM).
 - MFM-32 is a 32-item scale that measures motor function abilities that relate to daily functions. The total MFM-32 score is expressed as a percentage (range: zero to 100)

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of the maximum possible score, with higher scores indicating greater motor function. This scale is suitable for assessing gross and fine motor skills in children and adult patients.

- RULM is a 19-item scorable scale used to assess motor performance of the upper limb in ambulatory and non-ambulatory patients with SMA. It tests proximal and distal motor functions of both upper limbs. The total score ranges from zero (all the items cannot be performed) to 37 (all the activities are achieved fully without any compensatory maneuvers). Each item is scored from zero to two: zero= unable, one=able with modification, two=able with no difficulty. RULM is applicable to both children and adults with SMA.
- The primary efficacy outcome in SUNFISH Part Two was the change from baseline to Month 12 in the MFM32 score in risdiplam (Evrysdi) vs. placebo, which was 1.36 (95% CI 0.61, 2.11) vs. -0.19 (-1.22, 0.84), with a difference from placebo of 1.55 (95% CI 0.30, 2.81, p=0.0156). Key secondary outcomes in SUNFISH Part Two include the proportion of patients with a 3-point or greater change from baseline to Month 12 in the MFM32 total score in risdiplam (Evrysdi) vs. placebo, which was 38.3% (28.9, 47.6) vs. 23.7% (12.0, 35.4), with a difference from placebo of 2.35 (1.01, 5.44), p-value=0.0469; change from baseline in total score of RULM at Month 12 in risdiplam (Evrysdi) vs. placebo of 1.61 (1.00, 2.22) vs. 0.02 (-0.83, 0.87), with a difference from placebo of 1.59 (0.55, 2.62), p-value=0.0469.

VI. While primary endpoint was measured at Month 12, patients showed improvement at Month 6. In FIREFISH Part Two, 38 of 41 infants surpassed responder threshold (≥ 4 -point CHOP-INTEND improvement) at Month 6. Moreover, at Month 12, the same number of infants (38 of 41) achieved ≥ 4 -point CHOP-INTEND improvement. SUNFISH Part Two had follow-up visits every five weeks and appeared to significantly show greater changes in MFM32 from baseline compared to placebo starting at week 16.

VII. RAINBOWFISH is an ongoing phase 2 open-label, single-arm study designed to assess efficacy and safety of risdiplam (Evrysdi) in infants less than two months of age with pre-symptomatic SMA. The primary endpoint will assess the efficacy of risdiplam (Evrysdi) in infants with two *SMN2* copies and CMAP ≥ 1.5 mV at baseline based on the ability to sit without support for at least 5 seconds as measured by Item 22 of the Gross Motor Scale of the BSID-III after 12 months on treatment. Secondary endpoints will evaluate all enrolled infants (regardless of *SMN2* copy number) on the development of clinical symptoms of SMA, achievement of motor milestones as defined in the BSID-III and the HINE-2, ability to swallow and feed orally, CHOP-INTEND motor function scale, growth measures, and time to permanent ventilation and/or death.

- A total of 26 patients with pre-symptomatic SMA are currently enrolled and preliminary data (data cut off July 2021) is available for 7 patients (four patients had 2 copies of the *SMN2*, two patients had 3 copies, and one patient had >4 copies) treated with risdiplam (Evrysdi) for at least 12 months. Interim efficacy data showed patients treated with risdiplam (Evrysdi) achieved motor milestones (measured by the HINE-2) within WHO windows for healthy children at 12 months. All seven patients were alive at 12 months without permanent ventilation, achieved sitting without support, were able to feed exclusively by mouth, and maintained the ability to swallow solid food. In the six patients with two or three copies of the *SMN2* genes, four patients (67%) were able to stand and 3 patients (50%) were able to

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walk independently at month 12. Interim safety data is consistent with the safety profile of risdiplam (Evrysdi) for pediatric and adult patients with symptomatic SMA. The most common adverse events included teething (33%), nasal congestion (28%), and pyrexia (28%). There were no reported deaths or treatment-related adverse events that led to withdrawal at data cut off. No treatment related serious adverse events were reported in patients treated for up to 22.8 months. Full efficacy and safety data RAINBOWFISH has not been published.

- VIII. Baseline documentation of motor function/milestones for patients younger than 2 months of age proactively requesting risdiplam (Evrysdi) may not be available at the time of the request. To avoid delaying access to initial therapy in recently diagnosed infants, assessments completed shortly posttherapy may serve as baseline.
- IX. Other acceptable motor measurements not measured in risdiplam (Evrysdi) trials, but are validated are the following: Hammersmith Functional Motor Scale Expanded (HFMSE) and Six-Minute Walk Test (6MWT)
 - HFMSE is a 33-item scorable scale used to assess motor function in people with SMA Type II or Type III; this is intended for individuals older than 24 months of age. Each item is scored from zero (lowest item grade) to two (highest item grade), with a maximum score of 66. Higher scores indicate increased levels of ability. Scorable items include, but not limited to, plinth/chair sitting, long sitting, one to two hands to head in sitting, spine to side-lying, rolls prone to supine over right and left, rolls supine to prone over right and left, sitting to lying, props on forearms, lifts head from prone, prop on extended arms, lying to sitting, 4-point kneeling, crawling, and stepping.
 - 6MWT is an objective evaluation of functional exercise capability in ambulatory patients with later-onset (Type II or Type III) SMA. This test is based on distance where the patient walks as far as possible in six minutes; test is performed on a linear 25-meter marked course.
- X. As of December 2022, the International Conference on the Standard of Care for Spinal Muscular Atrophy guidelines have not been updated to include risdiplam (Evrysdi) for the treatment of SMA.
- XI. Per the Working Group for SMA-positive infants (comprised of 15 SMA experts), a pediatrician's expertise in child healthcare may be broad and not cover the unique features of a rare neuromuscular disorder; similarly, a general child neurologist may not specialize in the role of the neuromuscular system of the patient's symptomatology and diagnosis and may not have the knowledge to administer the specific tests being recommended here. A neuromuscular specialist would have the deepest knowledge of the clinical manifestations of SMA in order to detect the earliest symptomatology, in addition to experience with administering the highly sensitive assessments of motor neuron function and SMA specific motor function.
- XII. Nusinersen (Spinraza) is a chronic, intrathecally administered therapy and onasemnogene abeparvovec-xioi (Zolgensma) is a one-dose treatment. Use of risdiplam (Evrysdi) in patients (1-60 years of age) previously treated with approved or investigational therapies for SMA is currently being studied in the JEWELFISH trial. Forty-four (n=77) of those enrolled had previously been treated with nusinersen (Spinraza), 8% (n=14) with onasemnogene abeparvovec (Zolgensma), and the remaining 48% were previously treated with investigational therapies (RG7800* (n=13) and olesoxime* (n=71)). Out of the 14 patients previously treated with

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onasemnogene abeparvovec-xioi (Zolgensma), two enrolled in the trial due to lack of efficacy and eight enrolled to assess additional benefit after initial treatment. Interim exploratory efficacy data suggest stabilization in motor function measured by change from baseline in motor function measure (MFM-32) at 24 months of treatment and the overall adverse event profile of risdiplam (Evrysdi) has been consistent with that in treatment naïve patients; however data is limited. At this time, there is insufficient high-quality evidence to suggest the efficacy and safety of risdiplam (Evrysdi) in this patient population.

**RG7800 and olesoxime are no longer in development as investigational treatments for patients with SMA.*

Investigational Uses

- I. Risdiplam (Evrysdi) has not been FDA approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Use in members with Type IV SMA
 - i. Risdiplam (Evrysdi) has not be studied in this population.
 - B. Use in combination with nusinersen (Spinraza)
 - i. Risdiplam (Evrysdi) has not been studied to be used in combination use with nusinersen (Spinraza).
 - C. Use after treatment with onasemnogene abeparvovec-xioi (Zolgensma)
 - i. There is limited high quality evidence to suggest efficacy and safety of risdiplam (Evrysdi) in patients previously treated with onasemnogene abeparvovec-xioi (Zolgensma).

Appendix

- I. There are no specific contraindications or warnings and precautions to using risdiplam (Evrysdi)
- II. Table 1: risdiplam (Evrysdi) Adult and Pediatric Dosing Regimen by Age and Body Weight

Age and Body Weight	Recommended Daily Dosage
Less than 2 months of age	0.15mg/kg
2 months to less than 2 years of age	0.2 mg/kg
2 years of age and older weighing less than 20 kg	0.25 mg/kg
2 years of age and older weighing 20 kg or more	5 mg

References

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Related Policies

Currently there are no related policies.

Policy Implementation/Update

Action and Summary of Changes	Date
Added 5mg tablet to policy	02/2025
Updated supporting evidence and references regarding interim JEWELFISH study results.	12/2022
Modified criteria to limit coverage to patients not previously treated with onasemnogene abeparvovec-xioi to align with medical policies. Added prior treatment with onasemnogene abeparvovec-xioi to E/I. Updated supporting evidence.	09/2022
Updated criteria to include coverage in pre-symptomatic patients with two or three copies of SMN2 gene. Removed use in pre-symptomatic patients from E/I. Updated supporting evidence and references section.	06/2022
Policy created	11/2020

Policy Type: PA

Pharmacy Coverage Policy: UMP105

Description

Roflumilast (Daliresp) is an oral phosphodiesterase 4 (PDE4) inhibitor that selectively inhibits a cyclic-AMP (cAMP) metabolism in the lung tissue.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
generic roflumilast	To reduce the risk of Chronic Obstructive Pulmonary Disease (COPD) exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations	250 mcg tablet	Initial month: 30 tablets/30 days*
		500 mcg tablet	30 tablets/30 days
roflumilast (Daliresp)		250 mcg tablet	Initial month: 30 tablets/30 days*
		500 mcg tablet	30 tablets/30 days

*Coverage of 250 mcg daily dose limited to one month for medication titration; quantity exceptions not allowed.

Initial Evaluation

- I. **Roflumilast (Daliresp)** may be considered medically necessary when the following criteria are met:
 - A. Member is 18 years of age or older; **AND**
 - B. Diagnosis of severe or very severe COPD (GOLD 3 or 4; FEV₁ < 50% predicted); **AND**
 - C. Diagnosis of chronic bronchitis; **AND**
 - D. Member has a history of at least one COPD exacerbation in the past year; **AND**
 - E. Triple therapy with long-acting beta agonist (LABA), long-acting muscarinic antagonist (LAMA), and inhaled corticosteroid (ICS) has been ineffective, contraindicated, not tolerated or will be continued with roflumilast (Daliresp) [see appendix for examples]; **OR**
 1. Dual therapy with LABA and LAMA therapy has been ineffective, contraindicated, or not tolerated if eosinophil level is < 100 cells/uL; **AND**
 - F. At least one long-acting bronchodilator therapy (LAMA and/or LABA) will be continued in combination with roflumilast (Daliresp); **AND**
 - G. Request is for generic roflumilast (generic for Daliresp), unless member has a contraindication to generic product
- II. Roflumilast (Daliresp) is considered not medically necessary when criteria above are not met and/or when used for:

- A. Roflumilast (Daliresp) daily dose of 250 mcg for longer than the one-month initiation period for tolerability. This has been deemed a subtherapeutic dose by the drug manufacturer and FDA.
- III. Roflumilast (Daliresp) is considered investigational when used for all other conditions, including but not limited to:
 - A. Pediatric COPD
 - B. Asthma

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. The request is for roflumilast (Daliresp) 500mcg tablet; **AND**
- IV. Provider attestation of one of the following:
 - A. The member has exhibited stability or improvement in rate or severity of exacerbations or improvement in lung function; **OR**
 - B. Continuation of therapy is medically necessary despite lack of benefit in exacerbations or lung function (documentation is required).

Supporting Evidence

- I. Roflumilast (Daliresp) starting dose is 250 mcg per day to improve tolerability and reduce likelihood of discontinuation due to adverse effects; however, this dose is subtherapeutic. The 250 mcg tablets are administered once daily for four weeks; thereafter, 500 mcg daily is used for maintenance. A 250mcg daily maintenance or quantity exceptions to utilize two x 250 mcg tablets daily are not covered. The 500mcg tablet is administered once daily and has an extended half-life, eliminating the need for twice daily dosing. Additionally, the 500mcg tablet is more cost efficient.
- II. Roflumilast (Daliresp) is indicated to reduce the risk of COPD exacerbations in patients with severe or very severe COPD associated with chronic bronchitis and have a history of exacerbations. It has only been evaluated in adults; safety and efficacy are unknown when used in pediatrics. COPD does not normally occur in children and rare cases may be due to genetic conditions; however, roflumilast (Daliresp) has unknown consequences in these settings.
- III. Chronic bronchitis is defined as chronic productive cough for three months in each of two successive years in a patient whom other causes of chronic cough have been excluded.
- IV. Effects of roflumilast (Daliresp) have been evaluated in nine phase 3 clinical trials and other supplemental studies. The majority of trials failed to show clinical improvement in lung function, exacerbation rate, survival, or quality of life in the general COPD population. Exploratory analyses of early clinical trials identified a subpopulation of patients that appeared to demonstrate a better response to roflumilast (Daliresp); those with severe COPD associated with chronic bronchitis that have a history of COPD exacerbations within the last year. Several clinical trials have demonstrated lack of clinical benefit of roflumilast (Daliresp) in an unselected patient population with COPD. Given the lack of benefit outside of the FDA-approved population

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- coupled with specific safety concerns (e.g., psychiatric adverse effects including but not limited to suicide and suicidal ideation), coverage is limited to a narrow population.
- V. The FDA-approval for roflumilast (Daliresp) is based on trials five and six of the clinical program that demonstrated a modest reduction in exacerbations vs. placebo and a statistically significant, but non-clinically significant, increase in FEV1. Patients were allowed to be on LABA or short-acting muscarinic antagonist (SAMA) therapy, and all patients had at least one recorded exacerbation requiring systemic corticosteroids or hospital admission within the previous year.
 - VI. A Cochrane Systematic Review of PDE4 inhibitors for COPD was conducted in 2020 to evaluate the extensive evidence for roflumilast (Daliresp) and other non FDA-approved therapies in this class. The conclusions of the review are as follows: PDE4 inhibitors in people with COPD may have additional but limited value and act independently of bronchodilators in patients with COPD. These therapies have a small benefit over placebo in reducing lung function or reducing likelihood of exacerbations. There is no known impact on quality of life or symptom control; however, there is cautious support for use and the identified place in therapy is as add-on therapy for patients with persistent symptoms or exacerbations despite optimal COPD management.
 - VII. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2022 report stance: roflumilast (Daliresp) may reduce exacerbation rates in those with severe or very severe COPD with chronic bronchitis and a history of exacerbations – mirroring the FDA approved indication. It is noted that roflumilast (Daliresp) benefits may be greater in patients with a prior hospitalization for acute COPD exacerbation; however, it is unknown if the benefit is selective to those with prior exacerbation requiring hospitalization (subgroup analyses of trials signal a greater benefit in those with prior hospitalization). The GOLD report recommends the following therapy in patients with persistent exacerbations despite long-acting bronchodilator monotherapy:
 - Escalate to LABA/LAMA or LABA/ICS unless eosinophil level is < 100 cells/uL.
 - In those with exacerbation while on LABA/ICS: add a LAMA or switch to LABA/LAMA.
 - In those with exacerbation on either triple therapy LABA/LAMA/ICS or in those with exacerbation on dual therapy with LABA/LAMA for which ICS was inappropriate: roflumilast (Daliresp) may be added in the setting of severe or very severe disease, chronic bronchitis, and if patients have a history of exacerbation; particularly in those that have been hospitalized for an exacerbation in the previous year.
 - VIII. The Canadian Thoracic Society and European Respiratory Society/American Thoracic Society guidelines provide similar recommendations for use of roflumilast (Daliresp). Roflumilast (Daliresp) is not a bronchodilator therapy and should not be used for the relief of acute bronchospasm. It is not recommended to be used as monotherapy given lack of benefit in symptom control or quality of life, and the medication has unknown effects on exacerbation rate when used alone. It is recommended that dual or triple therapy be used prior to initiation of roflumilast (Daliresp) and that at least one bronchodilator (LABA and/or LAMA) be continued with roflumilast (Daliresp). It is also appropriate for roflumilast (Daliresp) to be added to triple therapy (LABA/LAMA/ICS). Some evidence suggests that roflumilast (Daliresp) may have additive effects with ICS; however, ICS may not be appropriate for all patients (e.g., not tolerated, low eosinophil level). When eosinophil levels are < 100 cells/uL, it is unlikely that ICS will be an effective therapy for patients with COPD and is not a required therapy under this condition.

When eosinophil level is adequate and tolerated, ICS is guideline recommended therapy prior to treatment initiation with roflumilast (Daliresp).

Investigational or Not Medically Necessary Uses

- I. Roflumilast (Daliresp) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below and are considered experimental and investigational:
 - A. Pediatric COPD
 - B. Asthma
- II. Roflumilast (Daliresp) daily dose of 250 mcg for longer than the one-month initiation period for tolerability is considered not medically necessary. This has been deemed a subtherapeutic dose by the drug manufacturer and FDA.

Appendix

- I. GOLD Classification of Airflow Limitation Severity in COPD
 - A. GOLD 1: Mild COPD, FEV1 is $\geq$ 80% predicted
 - B. GOLD 2: Moderate COPD, FEV1 is $\geq$ 50% predicted but $<$ 80% predicted
 - C. GOLD 3: Severe COPD, FEV1 is $\geq$ 30% predicted but $<$ 50% predicted
 - D. GOLD 4: Very Severe COPD, FEV1 is $<$ 30% predicted
- II. Long-acting beta agonists (LABA):
 - A. Formoterol (Foradil Aerolizer)
 - B. Salmeterol (Serevent Diskus)
 - C. Olodaterol (Striverdi Respimat)
 - D. Formoterol (Performist)
 - E. Arformoterol (Brovana)
 - F. May also be a part of combination inhalers: budesonide/formoterol (Symbicort), fluticasone/umeclidinium/vilanterol (Trelegy Ellipta), budesonide/glycopyrrolate/formoterol (Breztri Aerosphere), fluticasone/salmeterol (Advair, AirDuo, generic), fluticasone/vilanterol (Breo Ellipta), etc.
- III. Long-acting muscarinic antagonists (LAMA):
 - A. Umeclidinium (Incruse Ellipta)
 - B. Glycopyrrolate (Seebri Neohaler, Lonhala), aclidinium (Tudorza Pressair), tiotropium (Spiriva)
 - C. May also be a part of combination inhalers: umeclidinium/vilanterol (Anoro), tiotropium/olodaterol (Stiolto), glycopyrrolate/formoterol (Vespi), and glycopyrronium/indacaterol (Ultibron), etc.
- IV. Inhaled corticosteroids (ICS)
 - A. Mometasone (Asmanex)
 - B. Beclomethasone (Qvar)
 - C. Budesonide (Pulmicort)
 - D. Fluticasone (Flovent, Armonair)
 - E. May also be part of combination inhalers, see above, etc.

Related Policies

Currently there are no related policies.

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Policy Implementation/Update

Action and Summary of Changes	Date
Added renewal criterion to require maintenance dose of 500mcg tablet	04/2025
Added requirement to try and fail generic roflumilast prior to using branded Daliresp	10/2022
Allowance of 250 mcg dose limited to one month titration period; Removal of requirement of recent hospitalization; Reworded to include very severe COPD patients for coverage allowance; Update to allow bypassing of ICS when eosinophil level is < 100 cells/uL; Updated to require continuation of a long-acting bronchodilator; Removal of requirement to continue ICS; Addition of adult age requirement. Policy updated to current format with inclusion of supplementary sections: E/I, NMN, Appendix, Related Policies. Added detailed supporting evidence.	08/2022
Criteria transitioned to policy format, with the following changes: further clarification around severe COPD definition, dose limit that it does not exceed 500 mcg per day if request is for a dose increase, supporting evidences were updated, and GOLD 2020 Report was updated.	11/2019
Criteria created	04/2018

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP257

Split Fill Management*

Description

Ropeginterferon alfa-2b-njft (RIFN- α -2b; Besremi) is a long-acting, monopegylated, interferon alfa isomer which induces cellular activities related to binding specific cell-surface membrane receptors.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
ropeginterferon alfa-2b-njft (Besremi)	500 µg/mL pre-filled syringe (PFS)	Polycythemia Vera (PV)	2 syringes/28 days

Initial Evaluation

- I. **Ropeginterferon alfa-2b-njft (Besremi)** may be considered medically necessary when the following criteria are met:
 - A. Member is 18 years of age or older; **AND**
 - B. Medication is prescribed by, or in consultation with an oncologist or hematologist; **AND**
 - C. A diagnosis of **polycythemia vera (PV)** when the following are met:
 1. Provider attests that the member has high-risk PV and requires cytoreductive therapy; **AND**
 2. Treatment with both of the following has been ineffective or not tolerated, unless all are contraindicated:
 - i. Hydroxyurea
 - ii. Peginterferon alfa-2a (Pegasys); **AND**
 3. Ropeginterferon alfa-2b-njft (Besremi) is medically necessary for the treatment of polycythemia vera (PV) over hydroxyurea and peginterferon alfa-2a (Pegasys). (Note: preference for longer injection interval or other convenience does not meet medical necessity).
- II. Ropeginterferon alfa-2b-njft (Besremi) is considered investigational when used for all other conditions, including but not limited to:
 - A. Myelofibrosis

- B. Essential thrombocythemia
- C. Chronic hepatitis infection (e.g., hepatitis B, hepatitis C)
- D. Acute myeloid leukemia (AML)

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Member has exhibited disease improvement or stability (e.g., complete hematological response (CHR), improved hematocrit $\leq 45\%$, platelet and WBC counts within normal range).

Supporting Evidence

- I. RIFN- α -2b (Besremi) is FDA-approved for the treatment of adult patients with PV. PV is a rare, chronic, myeloproliferative disorder caused by a mutation in bone marrow stem cells resulting in blood cell overproduction. Symptoms include pruritis, fatigue, and microcirculatory disturbance. PV may progress to myelofibrosis and acute myeloid leukemia (AML).
- II. PV risk stratification is based on age and comorbidities. Patients ≥ 60 years at initial diagnosis and presence of cardiovascular comorbidities or thromboembolic event history are classified as high-risk. Risk level guides treatment. For low-risk PV, periodic phlebotomy combined with low-dose aspirin remain the first-line therapy. Patients with high-risk PV may require cytoreductive therapy. Additionally, low-risk PV patients, who are symptomatic after repeated phlebotomy may be considered as potential candidates for cytoreductive therapy. This may consist of patients who experience new thrombosis, splenomegaly, progressive thrombocytosis, or disease-related major bleeding event when being managed via phlebotomy. These patients, even though classified as low-risk PV cases, are recommended to be treated similar to high-risk PV. Cytoreductive therapy may be considered medically necessary in this subgroup of patients.
- III. The National Comprehensive Cancer Network (NCCN) guideline for the treatment of myeloproliferative neoplasms recommend hydroxyurea (HU) or peginterferon alfa-2a (Pegasys) as preferred cytoreductive agents. In practice, peginterferon alfa-2a (Pegasys) may be considered for younger patients, during pregnancy or where treatment with HU is contraindicated. For patients with intolerance or resistance to other cytoreductive agents, ruxolitinib (Jakafi) is a recommended subsequent-line therapy. As of March 2022, the NCCN guideline added RIFN- α -2b (Besremi) as 'other recommended regimen' (Category 2A) for the treatment of high-risk PV. Additionally, RIFN- α -2b (Besremi) may also be considered as another recommended regimen, when used adjunct to phlebotomy, for the initial treatment of low-risk PV. This recommendation is based on lower-level evidence (Category 2B). Current clinical data for RIFN- α -2b (Besremi) does not provide a high degree of confidence for use in the initial treatment of patients with low-risk PV, and cytoreductive treatment naïve patients.
- IV. FDA-approval is based on efficacy data from a single-arm, open-label Phase 1/2 clinical trial (PEGINVERA) and safety profile assessed via subsequent open-label, randomized, active-controlled Phase 3 trials (PROUD-PV, CONTINUATION-PV) in addition to PEGINVERA.

- Phase 1/2 study: patients (N=51) were newly diagnosed, had exposure to HU, any risk level disease, and refractory to phlebotomy. RIFN- α -2b (Besremi) led to an overall hematological response of 75% at week 10, with 26% reported as complete response (CR). Additionally, 74% patients achieved a Hct $\leq$ 45% at 12 months.
 - Phase 3 trials: Two concurrent randomized Phase 3 trials assessed RIFN- α -2b (Besremi) versus standard therapy (HU): PROUD-PV to assess non-inferiority of RIFN- α -2b (Besremi) to HU over 12 month regimen; CONTINUATION-PV: to assess CHR and improvement in disease burden at 36 months of therapy. Primary endpoint results for these trials were not statistically significant and non-inferiority to HU was not shown. However, RIFN- α -2b (Besremi) improved long-term disease response and CHR at 36 months vs. HU.
- V. Prescribing information for RIFN- α -2b (Besremi) includes a black box warning for fatal or life-threatening neuropsychiatric, autoimmune, ischemic and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations.
 - VI. For those with high-risk PV and require cytoreductive therapy, HU is the preferred first-line therapy given the extensive history of use, established safety profile, efficacy and cost-effectiveness. Although not FDA-approved for the treatment of PV, peginterferon alfa-2a (Pegasys) has found its place as an alternative cytoreductive agent, with supportive data from multiple clinical trials and retrospective studies. Notably, a Phase 2 open-label clinical trial assessed Pegasys for induction of CR and PR in patients with high-risk PV (n=50), where in overall response rate of 60% (22% CR) was reported. Additional Phase 3 clinical trial (N=168) also assessed efficacy of Pegasys vs. hydroxyurea and reported comparable response rates.
 - VII. Currently available clinical data does not conclusively establish superiority of RIFN- α -2b (Besremi) over HU. Although RIFN- α -2b (Besremi) is purported to provide better acute tolerability due to longer interval between injections (14 days) versus Pegasys (7 days), efficacy and safety of RIFN- α -2b (Besremi) has not been compared with peginterferon alfa-2a (Pegasys) in a head-to-head clinical trial. At this time, real-world safety profile and patient experience with RIFN- α -2b (Besremi) remain largely unknown. Thus, preference toward bi-weekly dosing or convenience of administration does not establish medical necessity of RIFN- α -2b (Besremi) over peginterferon alfa-2a (Pegasys). Weighing the safety, efficacy, cost, and clinical experience, HU and peginterferon alfa-2a (Pegasys) are considered standard and appropriate high-value cytoreductive treatment options for the treatment of PV.

Investigational or Not Medically Necessary Uses

- I. RIFN- α -2b (Besremi) has not been FDA-approved, or sufficiently studied for the treatment of any other condition, including other myeloproliferative neoplasms (e.g., essential thrombocythemia, myelofibrosis, acute myeloid leukemia (AML)).

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
peginterferon alfa-2a (Pegasys)	Polycythemia vera
	Essential thrombocythemia
	Chronic hepatitis B
	Chronic hepatitis D

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2022

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP152

Split Fill Management*

Description

Rucaparib (Rubraca) is an orally administered poly (ADP-ribose) polymerase (PARP) inhibitor indicated for the maintenance therapy, of ovarian, fallopian tube, or primary peritoneal cancer.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
rucaparib (Rubraca)	200 mg tablets	Maintenance for: recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer;	120 tablets/30 days
	250 mg tablets		
	300 mg tablets		

Initial Evaluation

- I. **Rucaparib (Rubraca)** may be considered medically necessary when the following criteria below are met:
 - A. Member is 18 years of age or older; **AND**
 - B. Medication is prescribed by, or in consultation with, an oncologist; **AND**
 - C. Rucaparib (Rubraca) will be used as monotherapy; **AND**
 - D. Member has not progressed on a prior PARP inhibitor (e.g., olaparib [Lynparza], niraparib [Zejula]) therapy; **AND**
 - E. A diagnosis of one of the following:
 1. **Recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer; AND**
 - i. Provider is requesting for maintenance therapy; **AND**
 - ii. Member has experienced disease progression on or after at least TWO or more prior platinum-based chemotherapy regimens (e.g., cisplatin, carboplatin, oxaliplatin); **AND**
 - iii. Member is in complete or partial response to their last platinum-based chemotherapy regimen (i.e., platinum sensitive); **AND**
 - iv. Rucaparib (Rubraca) will be started within eight weeks of completion of the most recent platinum-based chemotherapy regimen; **OR**
 - v. Provider attests with supporting documentation that member's recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer has not progressed since the most recent platinum-based chemotherapy regimen

- II. Rucaparib (Rubraca) is considered investigational when used for all other conditions, including but not limited to:
 - A. Used in combination with other chemotherapy or targeted therapy regimen
 - B. Breast Cancer
 - C. Prostate Cancer
 - D. Advance Solid Tumors
 - E. Melanoma
 - F. Pancreatic cancer
 - G. Gastroesophageal cancer
 - H. Treatment of advanced ovarian cancer after 3 of more lines of therapy

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Rucaparib (Rubraca) will be used as monotherapy; **AND**
- IV. Member has exhibited improvement or stability of disease symptoms (e.g., decrease in tumor size, or tumor spread).

Supporting Evidence

- I. The safety and efficacy of rucaparib (Rubraca) in the setting of maintenance therapy for recurrent ovarian cancer was studied in a double-blind, multicenter trial (ARIEL3) where 564 adult patients with platinum-sensitive recurrent epithelial ovarian fallopian tube or primary peritoneal cancer. The patients were randomized 2:1 rucaparib (Rubraca) 600 mg orally daily or matched placebo within 8 weeks of their last dose of platinum-based therapy. The major efficacy outcome was progression-free survival (PFS) assessed by investigator, which ARIEL 3 demonstrated a statistically significant improvement in PFS in the rucaparib (Rubraca) arm as compared to the placebo arm. In the rucaparib (Rubraca) arm, the median PFS was 10.8 months compared to 5.4 months in the placebo arm with a hazard ratio (HR) of 0.36 and 95% CI (0.3, 0.45).
- II. Therapy in the maintenance setting was initiated within eight weeks after completion of the last dose of platinum-based chemotherapy. The intent is that treatment is started within a reasonable timeframe consistent with a maintenance treatment plan (i.e., as close to 8 weeks as possible), but recognize that scheduling or other factors may impact the ability of a patient to start exactly within these first eight weeks.
- III. There is a lack of strong scientific evidence from randomized controlled trials supporting safety and efficacy to support the use of a subsequent PARP inhibitor following progression of disease on another PARP inhibitor.

Investigational or Not Medically Necessary Uses

- I. There is a lack of strong scientific evidence from randomized controlled trials supporting safety and efficacy for the use of rucaparib (Rubraca) in the following settings listed below:
 - A. Used in combination with other chemotherapy or targeted therapy regimen.
 - B. Breast Cancer
 - C. Solid Tumors
 - D. Prostate Cancer
 1. Efficacy of rucaparib (Rubraca) was investigated in an ongoing multi-center, single arm clinical trial (TRITON2) in patients with *BRCA*-mutated metastatic castration-resistant prostate cancer (mCRPC), who had been treated with androgen receptor-directed therapy and taxane-based chemotherapy. There were 115 patients with either germline or somatic *BRCA* mutations enrolled in TRITON2, of whom 62 patients had measurable disease at baseline. Patients received rucaparib (Rubraca) 600 mg orally twice daily along with concomitant GnRH analog or had prior bilateral orchiectomy. Objective response rate (ORR) and duration of response (DOR) were assessed in patients with measurable disease by blinded IRR and by the investigator protocol. An ORR of 43.5% (n= 27; 31.0-56.7) was reported for IRR evaluation of 62 patients with measurable disease, while DoR was not estimable given the lack of data maturity. Quality of clinical evidence is low due to open label, single-arm trial design and lack of measurable survival outcomes and patient quality of life related outcomes. Of note, as of October 2020, rucaparib (Rubraca) is being studied in a phase 3 trial for mCRPC with other therapeutic agent(s) as active comparator (TRITON3) and results for this study are not available. Of note, another PARP-inhibitor, olaparib (Lynparza) is FDA-approved for treatment of mCRPC in patients who progressed on previous chemotherapy. Olaparib (Lynparza) was approved for this indication based on an open label phase 3 trial, which reported survival outcomes (rPFS and OS) and has a category 1 recommendation per NCCN guidelines for treatment of prostate cancer.
- E. Treatment of advanced ovarian cancer after 3 or more lines of therapy
 1. The safety and efficacy of rucaparib (Rubraca) for the treatment of advanced ovarian cancer after two or more chemotherapies was studied in two multicenter, single-arm, and open-label trials with 106 adult patients that have advanced *BRCA*-mutant ovarian cancer who had progressed after two or more prior chemotherapies. The efficacy outcomes were objective response rate (ORR) and duration of response (DOR) assessed by the investigator and independent radiology review; the average ORR was 54% and the average DOR was 9.2 months.
 2. In June 2022, the manufacturer of rucaparib (Rubraca) voluntarily withdrew the indication for treatment of adult patients with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with 3 or more prior chemotherapy regimens. This withdrawal was based on a totality of information from PARP inhibitors in the late line treatment setting in ovarian cancer. Specifically, following data from the Ariel4 postmarketing trial linking rucaparib (Rubraca) to an increased risk of death over chemotherapy in patients with third-line or later ovarian cancer despite the drug showing a benefit in stalling disease progression. Similar detrimental effects on overall

survival were observed with another PARP inhibitor in a randomized, active-controlled clinical trial conducted in a BRCA mutant 3L+ advanced ovarian cancer population.

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References

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2. Coleman RL, Oza AM, Lorusso D, et al. Rucaparib Maintenance Treatment for Recurrent Ovarian Carcinoma After Response to Platinum Therapy (ARIEL3): A Randomized, Double-blind, Placebo-controlled, Phase 3 Trial. *Lancet*. 2017 Oct 390(10106): 1949–1961.
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Policy Implementation/Update:

Action and Summary of Changes	Date
Removal of ovarian cancer indication in the late line (3+) treatment setting following voluntarily withdraw of the indication by the manufacturer.	09/2022
Added split fill restriction given dose interruption/dose reduction rates. Corrected published QL to reflect 120/30. Confirmation of monotherapy use upon renewal.	08/2021
Updated supporting evidence for investigational use of rucaparib (Rubraca) for treatment of prostate cancer	11/2020
Criteria transition into policy with the following updates made: addition of supporting evidence and investigation section, broke out the different indications (treatment versus maintenance therapy), included mutation status for the treatment of recurrent ovarian cancer, included criterion around prior PARP inhibitor use, increase initial approval duration from three months to six months to be consistent with other payers, included age criterion per label, and removed the 8 weeks criterion around most recent platinum-based therapy in the setting of maintenance therapy in recurrent ovarian cancer; in place of the 8 weeks criterion, provider attestation and documentation is required instead.	12/2019

Policy Type: PA (Jakafi SP) Pharmacy Coverage Policy: UMP057

Split Fill Management* (applies to oral ruxolitinib [Jakafi] only)

Description

Ruxolitinib is a Janus Associated Kinase (JAK) inhibitor of JAK1 and JAK2. Ruxolitinib (Jakafi) is orally administered, and ruxolitinib (Opzelura) is a topical cream.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indications	Quantity Limit
ruxolitinib (Jakafi)	5 mg tablets	Intermediate or high-risk myelofibrosis	60 tablets/30 days
	10 mg tablets		
	15 mg tablets		
	20 mg tablets	Polycythemia vera	*Quantity exceptions are not allowed.
	25 mg tablets		
	5 mg tablets	Acute Graft-Versus-Host Disease	*The maximum number of ruxolitinib (Jakafi) tablets allowed is 60 tablets/30 days total if a combination of strengths is used
	10 mg tablets	Chronic Graft-Versus-Host disease	
ruxolitinib (Opzelura)	1.5 % cream	Atopic dermatitis	2 tubes/28 days (120 grams)
		Nonsegmental Vitiligo	

**Dose optimization will be required if the prescribed dose is unable to be reached at a quantity of 60/30. Use of two strengths may be necessary to reach target dose. Quantity is subject to 30/30 if multiple tablet strengths are utilized, for a maximum total allowed quantity of 60 ruxolitinib (Jakafi) tablets per 30-day supply.*

Initial Evaluation

- I. **Ruxolitinib (Jakafi)** may be considered medically necessary when the following criteria are met:
 - A. Medication is prescribed by, or in consultation with, an oncologist, hematologist, dermatologist, or immunologist; **AND**
 - B. A diagnosis of one of the following:
 1. **Intermediate-to-high-risk myelofibrosis (MF)** which includes primary MF, post-polycythemia vera MF, or post essential thrombocythemia MF; **OR**
 2. **Polycythemia vera; AND**
 - i. Treatment with hydroxyurea has been ineffective, contraindicated, or not tolerated; **OR**
 3. **Graft versus-host disease (GVHD), acute or chronic; AND**

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- i. Member is 12 years of age or older; **AND**
 - ii. Documentation of moderate-to-severe GVHD (e.g., Grade 2 to 4 GVHD, OR Grade B to D); **AND**
 - iii. The member has had an inadequate response to steroids (e.g., prednisone, methylprednisolone, beclomethasone, budesonide).
- II. **Ruxolitinib (Opzelura)** may be considered medically necessary when the following criteria are met:
 - A. Member is 12 years of age or older; **AND**
 - B. A diagnosis of one of the following:
 - 1. **Atopic Dermatitis; AND**
 - i. Treatment with at least one agent from two of the following groups have been ineffective, contraindicated, or not tolerated:
 - a. Group 1: topical corticosteroids (e.g., hydrocortisone, desonide, triamcinolone, betamethasone, clobetasol)
 - b. Group 2: topical calcineurin inhibitors: tacrolimus (e.g., Protopic), pimecrolimus (e.g., Elidel)
 - c. Group 3: topical phosphodiesterase 4 inhibitor: crisaborole (Eucrisa); **AND**
 - ii. Provider attestation that the member will NOT use topical ruxolitinib (Opzelura) in combination with systemic JAK inhibitors (e.g., baricitinib [Olmiant], upadacitinib [Rinvoq], abrocitinib); **OR**
 - 2. **Nonsegmental Vitiligo; AND**
 - i. Chronic disease (greater than 6 months); **AND**
 - a. A total body surface area that does **not** exceed 10%; **OR**
 - b. Involves areas of the face, ears, or genitalia; **AND**
 - ii. Treatment with at least one therapy from two of the following categories has been ineffective or not tolerated, or are contraindicated:
 - a. Phototherapy (UVB or PUVA); **OR**
 - b. Topical calcineurin inhibitors: tacrolimus (e.g., Protopic), pimecrolimus (e.g., Elidel); **OR**
 - c. Topical corticosteroids of at least high potency (e.g., betamethasone, mometasone, clobetasol, fluocinonide).; **AND**
 - iii. Provider attestation that the member will NOT use topical ruxolitinib (Opzelura) in combination with other biologics, systemic JAK inhibitors (e.g., baricitinib [Olmiant], upadacitinib [Rinvoq], abrocitinib), or potent immunosuppressants (e.g., azathioprine, cyclosporine).
- III. Ruxolitinib (Jakafi, Opzelura) is considered investigational when used for all other conditions, including but not limited to:
 - A. Low risk myelofibrosis
 - B. Acute leukemia
 - C. COVID-19
 - D. Alopecia areata
 - E. Other vitiligo diseases outside of nonsegmental or other depigmentation disease
 - F. Glioma and glioblastoma

- G. Hidradenitis suppurativa
- H. Malignancy or cancer outside of myelofibrosis

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. For **intermediate- to high-risk myelofibrosis (MF) OR polycythemia vera:**
 - A. Request is for ruxolitinib (Jakafi); **AND**
 - 1. Documentation of reduction in spleen volume; **OR**
 - 2. Provider attestation of positive treatment response (e.g., improvement in symptoms, hematocrit control); **OR**
- IV. For **graft versus-host disease (GVHD), acute or chronic:**
 - A. Request if for ruxolitinib (Jakafi); **AND**
 - 1. Provider attestation of positive treatment response (e.g. reduction in symptoms associated with GVHD: gastrointestinal, ophthalmic, cutaneous, pulmonary); **OR**
- V. For **atopic dermatitis:**
 - A. Request is for ruxolitinib (Opzelura) topical treatment:
 - 1. Member has exhibited improvement or stability of disease symptoms (e.g., improvement in IGA score from baseline, reduction in BSA involvement, pruritis symptom reduction); **AND**
 - 2. Provider attestation that the member will NOT use topical ruxolitinib (Opzelura) in combination with systemic JAK inhibitors (e.g., baricitinib [Olumiant], upadacitinib [Rinvoq], abrocitinib).
- VI. For **nonsegmental vitiligo:**
 - A. Request is for ruxolitinib (Opzelura) topical treatment:
 - i. Member has exhibited improvement or stability of disease symptoms (e.g., improvement in F-VASI and/or T-VASI score from baseline, reduction in BSA involvement, depigmentation reduction); **AND**
 - ii. Provider attestation that the member will NOT use topical ruxolitinib (Opzelura) in combination with other biologics, systemic JAK inhibitors (e.g., baricitinib [Olumiant], upadacitinib [Rinvoq], abrocitinib), or potent immunosuppressants (e.g., azathioprine, cyclosporine).

Supporting Evidence

- I. Length of authorization for initial approval is six months due to the clinical trial design, efficacy was evaluated at 24 weeks or less for all indications. Additionally, therapy beyond six months of treatment should be reserved for those where benefits outweigh the risks. For ruxolitinib (Jakafi) If no treatment response is seen at six months, therapy should be tapered into discontinuation. Therapy should not be abruptly discontinued given the potential for symptom proliferation and exacerbation.
- II. The FDA-approved conditions for this therapy require specialized and individualized care and monitoring; thus, a specialist prescriber, or consultation with a specialist, is required.

- III. Treatment for MF is based on risk. For intermediate-to high risk MF, stem cell transplant is the recommended treatment option; however, for those ineligible for stem cell transplant, hydroxyurea, fedratinib (Inrebic), and ruxolitinib (Jakafi) are available treatment options. While hydroxyurea may relieve splenomegaly and some symptoms of the condition (e.g., thrombocytosis, leukocytosis), it is thought to be less efficacious than other treatment options and may not be beneficial for major symptoms of the condition.
- IV. Polycythemia vera treatment selection is also based on risk. Phlebotomy and/or low-dose aspirin are used in the management of low-risk disease. For high-risk disease, hydroxyurea is the preferred therapy given the extensive history of use, well-established safety profile, efficacy, and cost-effectiveness. Although busulfan has been used historically as a second-line therapy, because it has been associated with safety concerns such as cytopenia, pulmonary fibrosis, leukemia, and others, hydroxyurea remains the mainstay therapy. Ruxolitinib (Jakafi) is reserved for those that are not candidates for, or are refractory to, hydroxyurea, given the limited long-term safety and efficacy data. Additionally, for the treatment of polycythemia vera, ruxolitinib (Jakafi) is specifically FDA-approved after inadequate response or intolerance to hydroxyurea.
- V. The FDA approval of ruxolitinib (Jakafi) in the setting of intermediate-to high-risk myelofibrosis was based on the results of two randomized Phase 3 trials. In Study 1, the primary endpoint was the proportion of participants achieving greater than, or equal to, a 35% reduction from baseline in spleen volume at Week 24. Secondary outcomes included proportion of patients achieving a 50% or greater reduction in Total Symptom Score from baseline to week 24. This was measured by the modified Myelofibrosis Symptom Assessment Form (MFSAF), which incorporates abdominal discomfort, pain, night sweating, itching, bone and muscle pain, and early satiety. The study met statistical significance in all outcomes. In Study 2, the primary endpoint was the proportion of participants achieving greater than, or equal to, a 35% reduction from baseline in spleen volume at Week 48. This outcome was statistically significant.
- VI. The FDA approval of ruxolitinib (Jakafi) in the setting of polycythemia vera was based on the result of a randomized, open-label, active-controlled Phase 3 study. The primary endpoint was the proportion of participants at Week 32 achieving hematocrit control in the absence of phlebotomy and spleen volume reduction. In the ruxolitinib (Jakafi) arm, 60% of the participants met the primary endpoint compared to 19% in the placebo arm. Participants must have had a resistance or intolerance to hydroxyurea.
- VII. Graft-versus-host disease is a complication of allogeneic hematopoietic cell transplant. Treatment is dependent on severity and location of disease. The GVHD Grade depends on severity and location, and ranges from I-IV. Grade I is reflective of skin involvement, Grade IV is severe disease with severe skin involvement (e.g., blistering) and internal organ involvement, and Grade II-IV correlate with moderate to severe disease. The International Bone Marrow Transplant Registry Severity Index uses Grade A-D, which align with grading I-IV.
- VIII. For Grade I or A, or mild disease, topical therapy is indicated. For Grade II or B or greater, or moderate-to-severe disease, systemic therapy is warranted. Glucocorticoids are the mainstay therapy; however, for those with glucocorticoid resistant disease, participation in clinical trials is recommended as there is currently no consensus on standard of care. Otherwise, therapies such as ruxolitinib (Jakafi) or ibrutinib (Imbruvica) are recommended. Therapy such as mycophenolate, rituximab, etanercept (Enbrel), everolimus, and others have been used

historically, but there is lack safety and efficacy data from clinical trials to support the use of these therapies.

- IX. The FDA approval of ruxolitinib (Jakafi) in the setting of acute GVHD was based on the results of an open-label, single-arm, multicenter study in participants with steroid-refractory acute GVHD Grades II to IV that were 12 years of age or older. Therapy was evaluated up to 10 mg twice daily. The efficacy of ruxolitinib (Jakafi) was based on a Day-28 overall response rate (ORR) by the Center for International Blood and Marrow Transplant Research (CIBMTR) criteria and the duration of response. The ORR was 57.1% with a median duration response of 16 days.
- X. For chronic GVHD, ruxolitinib (Jakafi) was evaluated in a Phase 3, open-label, randomized trial against best available treatment (BAT). Patients were 12 years of age or older, steroid-refractory, and had moderate-to-severe disease. Outcomes were ORR, failure-free survival (FFS), and Lee Symptom Score. Ruxolitinib (Jakafi) was superior to BAT in all outcomes. Given the availability of objective and subjective positive outcomes in this condition, and lack of standard of care beyond glucocorticoids, there is moderate confidence that ruxolitinib (Jakafi) provides clinical value for this condition.
- XI. To date, ruxolitinib (Jakafi) has not been shown to improve survival for any condition.
- XII. The safety and efficacy of ruxolitinib (Jakafi), or any other JAK inhibitor has not been evaluated in patients under 12 years of age.
- XIII. Split fill applies to ruxolitinib (Jakafi) given the high rates of treatment discontinuation due to adverse events, and the rates of dose reduction or interruption seen in clinical trials (e.g., in the pivotal trial for aGVHD the rate of treatment discontinuation due to adverse events was 31%).
- XIV. Topical ruxolitinib is the first non-oral JAK inhibitor for the treatment of atopic dermatitis (AD). Emerging data are showing JAK inhibitors to be effective therapies; however, competing JAK therapies are oral systemic treatments: abrocitinib, upadacitinib (Rinvoq), and baricitinib (Olmiant).
- XV. Nonpharmacologic treatment options for mild-to-moderate AD include emollients, wet wrap therapy, and phototherapy. Topical pharmacologic treatment options include corticosteroids (TCS), calcineurin inhibitors (TCI) (e.g., tacrolimus, pimecrolimus), and phosphodiesterase-4 inhibitor crisaborole (Eucrisa). Choice of therapy is dependent on severity, location, and other patient factors (e.g., allergies, age).
- XVI. Ruxolitinib (Opzelura) was evaluated in two Phase 3, randomized, double-blind, vehicle-controlled studies in 872 adolescents and adults (TRuE-AD1 and TRuE-AD2) age 12 and older. Treatment arms: vehicle, ruxolitinib 0.75% or 1.5%. Treatment was used continuously for eight weeks, then patients from the vehicle arm were re-randomized 1:1 to ruxolitinib 0.75% or ruxolitinib 1.5% for an additional 44 weeks. Trial population characteristics included: At least 12 years of age, 60% were female, 70% were white, had a mean affected BSA of 9-10%, baseline EASI of 8, 75% of patients had an IGA of 3, a mean NRS score of 5, median duration of AD of 16 years, and 40% of patients had facial involvement.
- XVII. The primary outcome was proportion of patients achieving IGA treatment success (IGA-TS) (i.e., IGA score of 0 or 1 with at ≥ 2 grade improvement). Secondary outcomes were EASI75, change in EASI, and proportion of patients achieving ≥ 4 -point improvement in the NRS itch score. At eight weeks, both ruxolitinib arms showed statistical and clinical superiority to vehicle in all outcomes. The 52-week assessments showed similar, or favorable outcomes.

- XVIII. At eight weeks, rates of adverse events (AE) were similar among all treatment arms and were mild or moderate in severity. Common AE were burning ($\leq 6.5\%$) and pruritis (3.2%). Discontinuation rates due to AE were $\leq 4\%$. Safety data out to 52 weeks did not reveal additional safety warnings. No serious AE occurred as a result of ruxolitinib (Opzelura) treatment; however, there was a relatively small patient population evaluated, and with data only out to 52 weeks there may be unrealized safety characteristics. Although two clinical trials showed consistent improvement in the outcomes noted above, there remains uncertainty in the following: place in therapy, safety and efficacy data when used in combination with other topical therapies and/or systemic treatments for AD, long term safety, durability of efficacy, and comparative efficacy to other topical agents. The safety and efficacy profiles of other topical therapies are well established, and data are lacking to show superior safety and efficacy of ruxolitinib (Opzelura) over these agents. Furthermore, there is lack of safety and efficacy data in pediatric patients under 12 years of age. Other topical therapies have been approved in this age group, and ruxolitinib is being evaluated in this population.
- XIX. The safety profile of systemic JAKs is continuing to develop; however, the FDA has issued cardiovascular and malignancy warnings. The true safety profile of ruxolitinib (Opzelura) is unknown at this time, given the short trial duration and relatively small trial population. Utilizing a systemic JAK therapy in addition to topical JAK therapy has unknown, and potentially additive, risks. Until further data are available to establish a safety profile with this combination, dual use will be disallowed. For those in need of systemic and topical therapy, provider and patients should consider therapies and combination with alternative mechanisms, including, but not limited to, dupilumab, tralokinumab systemic therapies, and the aforementioned topical therapies.
- XX. Ruxolitinib (Opzelura) 1.5% topical cream is FDA-approved at a maximum of 60 grams per week, and medication should not be applied to greater than 20% of the body surface area. Additionally, therapy should be used for short term and non-continuous treatment of mild to moderate atopic dermatitis. A quantity limit of two tubes (120 grams total) per 28-day supply should be sufficient or better for the majority of patients to utilize this therapy. Upon initial trial of medication, quantity limits will be set at two tubes per 28-day supply to ensure appropriate utilization within FDA label (e.g., non-continuous use), as well as ensure patients realize efficacy with medication and to minimize medication waste in the event therapy is not effective.
- XXI. Ruxolitinib (Opzelura) was evaluated in two phase 3, randomized, double-blind, vehicle-controlled studies in 674 adolescents and adults (TRuE-V1 and TRuE-V2) age 12 and older. Treatment arms: vehicle, ruxolitinib 1.5%. Subjects were randomized 2:1 of ruxolitinib to vehicle and used continuously twice a day for 24 weeks, then an additional 28 week extension where all subjects received ruxolitinib twice daily. Trial population characteristics included: At least 12 years of age, 53% were female, 82% were white, had mean depigmented areas of 1% F-BSA, mean affected total BSA of up to 7.4%, median duration of nonsegmental vitiligo of 14.8 years, and subjects were not permitted to use phototherapy during the trial period.
- XXII. The primary endpoint for both trials was percent of patients to achieve decrease of at least 75% from baseline in the facial vitiligo area scoring index (F-VASI: takes into account level of depigmentation and lesion integrity) at week 24. Secondary endpoints included decrease of at least 50% in F-VASI, a decrease of at least 90% in F-VASI, decrease of 50% in total vitiligo area scoring index (T-VASI), change in VNS rating, and percentage change of total facial BSA affected.

- XXIII. The adverse events (AE) at week 24 were similar across both treatment groups, with the most common AE related to the trial drug were acne (5.4%) and pruritis (5.0%). Discontinuation rates from AE were <1%. Additional reporting of safety data after the extension period (week 52) found no additional safety concerns. AEs were similar to AEs noted in atopic dermatitis studies. There were 14 cases of serious AEs: 8 in the TRuE-V1 and 6 in the TRuE-V2. Review of supplemental data indicates most AEs resolved and no direct correlation to use of medication. 3 serious AEs that are ongoing include a subacute cord degeneration, prostate cancer, and papillary thyroid cancer. Overall, the two trials indicated improvement in the endpoints, there is still uncertainty in place of therapy, safety and efficacy in combination with other topical therapies for vitiligo, long term safety and efficacy against other topical agents. The safety and efficacy profiles of other topical therapies are well established, and data are lacking to show superior safety and efficacy of ruxolitinib (Opzelura) over these agents. There is a lack of safety and efficacy data in pediatric patients under 12 years of age and other topical therapies have been approved in this age group. There are ongoing extension studies assessing long term safety and efficacy past 52 weeks for 12 years of age and up but as of this time, it is not being evaluated for patients younger than 12 years of age with vitiligo.
- XXIV. Several international guidelines across different countries (Britain, Canada, Europe) align with AAD recommendations that consider topical corticosteroids (CS), topical calcineurin inhibitors and phototherapy as first-line treatment options. Topical CS can be used long-term in intermittent scheduling. Topical calcineurin inhibitors have the added benefit for use in sensitive areas of the body. Phototherapy remains an essential option for repigmentation and is recommended across all guidelines. All but one guideline recommendation discusses the availability of topical ruxolitinib (Opzelura), however they do not discuss placement in therapy and consider all options at parity.
- XXV. Additional options that are available outside of topical agents include use of systemic immunotherapy, surgical grafting, laser therapy and cryotherapy. These options are considered in exceptional circumstances such as treatment-resistant or extensive disease.
- XXVI. According to AAD guidelines for the treatment of atopic dermatitis, TCIs may be preferable to TCS in patients with recalcitrance to steroids, sensitive areas involved, steroid-induced atrophy, and long-term uninterrupted topical steroid use.
- XXVII. Treatment for moderate to severe disease includes the same topical classes noted above and, for those not amenable to topical, systemic immunosuppressants (e.g., corticosteroids, cyclosporine, methotrexate, azathioprine, mycophenolate mofetil), JAK inhibitors (e.g., abrocitinib, upadacitinib), and dupilumab (Dupixent), a biologic IgG4 that is FDA-approved for pediatrics and adults as a biologic option for moderate-to-severe atopic dermatitis. Currently, there are no head to head trials evaluating safety and/or efficacy differences or superiority between biologic therapies in atopic dermatitis. Dupilumab (Dupixent) has an established safety and efficacy profile for the treatment of atopic dermatitis and is approved down to six years of age. Upadacitinib (Rinvoq) has been evaluated and is FDA approved in patients down to 12 years of age. Abrocitinib (Cibinqo) is FDA approved in adult patients only.
- XXVIII. There may be patient specific scenarios in which the use of additional topical agents following failure of one class of topical agents would be impractical. Insight from dermatology specialists indicate that patients who have at least 15% BSA involvement, or involvement in sensitive areas (e.g., eyelids, axilla, genitals, gluteal cleft), and have severe disease are potential candidates for

systemic biologic therapy. Severe disease, as defined by NICE guidelines, includes widespread areas of dry skin, incessant itching, redness (with or without excoriation, extensive skin thickening, bleeding, oozing, cracking, and alteration of pigmentation), and severe limitation of everyday activities and psychosocial functioning, nightly loss of sleep; severe disease can also be classified as physician's global assessment (PGA) score of 4.0. Additionally, administration of topical agents may become impractical for patients with high disease burden (BSA $\geq$ 20%), considering twice daily administration is necessary for non-steroid topical agents for optimal efficacy.

Investigational or Not Medically Necessary Uses

- I. Ruxolitinib (Jakafi, Opzelura) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Low risk myelofibrosis
 - B. Acute leukemia
 - C. COVID-19 or associated symptoms or complications
 - D. Alopecia areata
 - E. Other vitiligo diseases outside of nonsegmental or other depigmentation disease
 - F. Glioma and glioblastoma
 - G. Hidradenitis suppurativa
 - H. Cancer or malignancy outside of myelofibrosis

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

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Policy Implementation/Update:

Action and Summary of Changes	Date
Updated criteria for Opzelura in setting of atopic dermatitis from step through trial of three agents to two topical agents. Updated criteria for Opzelura in setting of vitiligo from step through trial of all agents to step through trial of two agents.	08/2024
Added criteria for nonsegmental vitiligo	12/2022
Added ruxolitinib cream (Opzelura) policy criteria and supportive evidence for use in nonsegmental vitiligo. Updated E/I to reflect removal of nonsegmental vitiligo and maintain others as excluded.	11/2022
Added new indication of nonsegmental vitiligo for Opzelura noting this is an excluded indication.	09/2022
Ruxolitinib cream added into the policy for the treatment of atopic dermatitis.	08/2021
Chronic graft vs. host disease indication added to policy. Update of qualifying prescribers and appropriate doses and quantities per indication. Removal of infection free requirement, check of unacceptable toxicity, and requirement for previous use of hydroxyurea in myelofibrosis.	06/2021
Addition of acute graft vs. host disease indication to renewal section.	01/2020
Criteria transitioned to policy. Added newly FDA approved indication of acute graft versus host disease. Remove diagnostic questions, interaction questions, lab value questions. Added requirement for previous use of hydroxyurea prior to coverage of Jakafi for the indication of polycythemia vera.	07/2019
Previous reviews	12/2014, 12/2012, 07/2012, 05/2012

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP209

Description

Satralizumab-mwge (Enspryng) is an IL-6 monoclonal antibody subcutaneous injection.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
satralizumab (Enspryng)	120 mg/mL Prefilled Syringe	Neuromyelitis optica spectrum disorder (NMOSD)	Initial: 2 mL (pens) per 28 days for one fill Maintenance: 1 mL (pen) per 28 days

Initial Evaluation

- I. Satralizumab (Enspryng) may be considered medically necessary when the following criteria are met:
 - A. Member is 18 years of age or older; **AND**
 - B. Medication is prescribed by, or in consultation with, a neurologist; **AND**
 - C. Provider attestation the medication will not be used in combination with other biologic therapies (e.g., ravulizumab-cwvz [Ultomiris], tocilizumab [Actemra], eculizumab [Soliris], inebilizumab [Uplinza]) used to treat inflammatory conditions; **AND**
 - D. Documentation of a confirmed diagnosis of **neuromyelitis optica spectrum disorder (NMOSD)** when all of the following are met:
 1. The member is positive for anti-aquaporin-4 (AQP4) IgG antibodies (i.e., seropositive) supported by chart note documentation or laboratory results; **AND**
 2. The member has a history of one or more relapses requiring rescue or acute treatment (e.g., glucocorticoids, plasma exchange); **AND**
 3. Glucocorticoids, azathioprine, and/or mycophenolate will be used in combination with satralizumab (Enspryng); **OR**
 - i. Treatment with ALL of the following has been ineffective, contraindicated, or not tolerated for long term maintenance therapy:
 - i. Glucocorticoids
 - ii. azathioprine
 - iii. mycophenolate; **AND**
 4. Treatment with rituximab (e.g. Rituxan) has been ineffective, contraindicated, or not tolerated

- II. Satralizumab (Enspryng) is considered not medically necessary when criteria above are not met and/or when used for:
 - A. NMOSD that is anti-aquaporin-4 (AQP4) IgG antibody negative (i.e., seronegative)
- III. Satralizumab (Enspryng) is considered investigational when used for all other conditions, including but not limited to:
 - A. Rheumatoid or other forms of arthritis
 - B. Cytokine release syndrome
 - C. Arteritis

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Medication is prescribed by, or in consultation with, a neurologist; **AND**
- IV. Provider attestation the medication will not be used in combination with other biologic therapies (e.g., tocilizumab [Actemra], eculizumab [Soliris], inebilizumab [Uplinza]) used to treat inflammatory conditions; **AND**
- V. Provider attestation of a positive response to therapy (e.g., stabilization of disease, relapse reduction, relapse-free)

Supporting Evidence

- I. Satralizumab (Enspryng) is FDA-approved for NMOSD, a rare inflammatory disorder characterized by severe, immune-mediated attacks on the optic nerves and spinal cord. Hallmark features include optic neuritis attacks, transverse myelitis, unexplained hiccups, nausea, vomiting, and somnolence. Patients experience relapses that have varying degrees of recovery over weeks to months. NMOSD was historically considered as a form of multiple sclerosis (MS); however, MS therapies are often ineffective in the setting of NMOSD and certain MS therapies may further exacerbate NMOSD. Thus, a definitive diagnosis from a specialty provider is warranted. The majority of patients are seropositive, and if test results show seronegative disease, patients should be retested or considered for a differential diagnosis. Seronegative disease is often treated similarly to seropositive NMOSD; however, biologic medications often lack efficacy in the seronegative population.
- II. NMOSD is often treated acutely with high-dose IV glucocorticoids, and if refractory – plasma exchange. Once a definitive diagnosis is made, long-term therapy is recommended in all patients. Long-term therapies that are FDA-approved include eculizumab (Soliris) and inebilizumab (Uplinza), which are both provider administered products. Other therapies that have been used historically and are often regarded as standard of care include glucocorticoids, azathioprine, mycophenolate, and rituximab (e.g., Rituxan). Additionally and increasingly, IV tocilizumab (Actemra) has been considered. The quality of data varies for these agents;

however, all have shown positive response on relapse rates for seropositive NMOSD. The safety profile, is also further defined, given the longevity and extent of use in patients relative to satralizumab (Enspryng).

- III. The efficacy and safety of satralizumab (Enspryng) was evaluated in two Phase 3, blinded, randomized, placebo-controlled trials, where treatment was administered at weeks zero, two, four, then four weeks thereafter. Population characteristics: seropositive and negative patients, majority female, an annualized relapse rate of 1.5 with at least one documented attack in the last 12 months, with a variety of treatment histories (e.g., glucocorticoids [GC], DMARDS, previous b-cell depleting therapy). Exclusions: history of anti-IL-6 therapy, alemtuzumab, total body irradiation, or bone marrow transplantation.
- IV. Trial one evaluated satralizumab (Enspryng) monotherapy versus placebo, and trial two evaluated against placebo with both groups adding treatment to background immunosuppressive therapy (glucocorticoids, mycophenolate, azathioprine, and various combinations). The use of satralizumab (Enspryng) in addition to other biologic therapies (e.g., tocilizumab [Actemra], eculizumab [Soliris], inebilizumab [Uplinza]) has not been evaluated for safety and/or efficacy. Additionally, there is evidence to show that use of two biologic therapies concurrently has demonstrated increased risk of serious infection.
- V. Adolescent patients were included in the second pivotal trial, ages 12 and older. There was a low number (n=7) enrolled and subgroup analyses did not show clinical efficacy. Although this analysis was likely underpowered, safety and efficacy in non-adult population remains unknown at this time and FDA-approval has been granted for adults only.
- VI. In both trials there was a positive response on relapse rates in the seropositive (anti-aquaporin-4 [AQP4] antibody-positive) population. Of note, there was a lack of statistically significant efficacy in the seronegative population. Secondary outcomes evaluated medication efficacy on other symptom control, quality of life, and caregiver burden; however, they were not statistically significant. Medication success may be measured as a reduction in or freedom from relapses.

Investigational or Not Medically Necessary Uses

- I. Satralizumab (Enspryng) did not show improvement in relapse rates in the seronegative NMOSD population. Given lack of efficacy and largely unknown safety profile for this therapy, use is not medically necessary at this time.
- II. Satralizumab (Enspryng) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Rheumatoid or other forms of arthritis
 - B. Cytokine release syndrome
 - C. Arteritis
 - i. IL-6 therapies (e.g., tocilizumab [Actemra]) have been FDA-approved for the conditions listed above; however, use of satralizumab (Enspryng) for these conditions remains experimental and investigational.

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Policy Implementation/Update:

Action and Summary of Changes	Date
Added Ultomiris as an example of biologic thereapies that cannot be used in combination with Enspryg	06/2024
Policy created	11/2020

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP081

Split Fill Management (Only Applies to enzalutamide [Xtandi], and abiraterone [Zytiga, Yonsa])*

Description

Darolutamide (Nubeqa), apalutamide (Erleada), and enzalutamide (Xtandi) are orally administered androgen receptor inhibitors. Abiraterone (Zytiga, Yonsa) is an androgen biosynthesis inhibitor of CYP17.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
darolutamide (Nubeqa)	Prostate cancer, non-metastatic, castration resistant	300 mg tablets	120 tablets/30 days
	Prostate cancer, metastatic, castration-sensitive		
apalutamide (Erleada)	Prostate cancer, non-metastatic, castration resistant	60 mg tablets	30 tablets/30 days
	Prostate cancer, metastatic, castration-sensitive	240 mg tablets	
enzalutamide (Xtandi)	Prostate cancer, castration resistant	40 mg capsules	120 capsules/30 days
	Prostate cancer, metastatic, castration-sensitive	40 mg tablets	120 tablets/30 days
	Prostate cancer, non-metastatic, castration sensitive	80 mg tablets	60 tablets/30 days
abiraterone (Yonsa)	Prostate cancer, metastatic, castration-resistant, in combination with methylprednisolone	125 mg tablets	120 tablets/30 days
abiraterone (generic Zytiga)	Prostate cancer, metastatic, castration-resistant, in combination with prednisone	250 mg tablets	120 tablets/30 days
	Prostate cancer, metastatic, castration-sensitive, in combination with prednisone	500 mg tablets	60 tablets/30 days
abiraterone (Zytiga)	Prostate cancer, metastatic, castration-sensitive, in combination with prednisone	250 mg tablets	120 tablets/30 days
	Prostate cancer, non-metastatic, castration sensitive, in combination with prednisone	500 mg tablets	60 tablets/30 days

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Initial Evaluation

- I. **Darolutamide (Nubeqa), apalutamide (Erleada), enzalutamide (Xtandi), or abiraterone (Zytiga, Yonsa)** may be considered medically necessary when the following criteria below are met:
 - A. The member is 18 years of age or older; **AND**
 - B. The medication is prescribed by, or in consultation with, an oncologist or urologist; **AND**
 - C. The member has **not** previously progressed on darolutamide (Nubeqa), apalutamide (Erleada), enzalutamide (Xtandi), OR abiraterone (Zytiga, Yonsa); **AND**
 - D. Darolutamide (Nubeqa), apalutamide (Erleada), enzalutamide (Xtandi), or abiraterone (Zytiga, Yonsa) will **not** be used in combination with any other oncologic medication with the exception of therapies outlined below (e.g., hormone suppression therapy, docetaxel for mCSPC, or PARP inhibitors [i.e., olaparib (Lynparza) and talazoparib (Talzenna)] for mCRPC); **AND**
 - E. The member has either had a bilateral orchiectomy OR ongoing hormone suppression (e.g., GnRH therapy) will be used concurrently; **AND**
 - F. A diagnosis of one of the following:
 1. **Non-metastatic castration resistant prostate cancer**, defined by evidence of disease progression despite therapy with a gonadotropin-releasing hormone analog (GnRH) or a bilateral orchiectomy; **AND**
 - i. The member has a PSA-doubling time of 10 months or less during continuous androgen-deprivation therapy or after bilateral orchiectomy; **AND**
 - ii. One of the following is prescribed: darolutamide (Nubeqa), apalutamide (Erleada), OR enzalutamide (Xtandi); **OR**
 2. **Non-metastatic castration sensitive prostate cancer; AND**
 - i. The member is in the high- or very high-risk group defined by:
 - a. Node positive; **OR**
 - b. Node negative; **AND**
 - i. The member has two of the following:
 1. Stage T3 or T4 tumor
 2. Gleason Score ≥ 8
 3. PSA ≥ 40 ng/mL; **OR**
 - c. Experienced PSA doubling time of <6 months or PSA concentration ≥ 20 ng/mL on androgen deprivation therapy (e.g. GnRH analogs); **AND**
 - ii. The request is for generic abiraterone 250 mg tablets and will be used in combination with ALL the following:
 - a. External beam radiotherapy (EBRT), unless contraindicated
 - b. Androgen deprivation therapy (ADT) (e.g. GnRH analogs)
 - c. Prednisone; **OR**
 - iii. The request is for generic abiraterone 500 mg tablets or brand abiraterone (Zytiga, Yonsa); **AND**
 - a. Documentation of clinical rationale why 250 mg tablets would not be an effective regimen (convenience of a larger tablet size does not meet medical necessity); **AND**

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- b. Treatment will be used in combination with EBRT (unless contraindicated), ADT, and prednisone; **OR**
 - iv. The request is for enzalutamide (Xtandi); **AND**
 - a. Documentation of intolerance or contraindication to generic abiraterone; **OR**
 - 3. **Metastatic castration resistant prostate cancer**, defined by evidence of disease progression despite therapy with a gonadotropin-releasing hormone analog (GnRH) or a bilateral orchiectomy; **AND**
 - i. The request is for generic abiraterone 250 mg tablets and will be used in combination with prednisone; **OR**
 - ii. The request is for generic abiraterone 500 mg tablets; **AND**
 - a. Documentation of clinical rationale why 250 mg tablets would not be an effective regimen (convenience of a larger tablet size does not meet medical necessity); **OR**
 - iii. The request is for brand abiraterone (Zytiga), brand abiraterone (Yonsa); **AND**
 - a. Documentation of intolerance or contraindication to generic abiraterone; **AND**
 - b. Will be used in combination with prednisone; **OR**
 - iv. The request is for enzalutamide (Xtandi); **AND**
 - a. Medication will be used as monotherapy **AND**
 - i. Documentation of intolerance or contraindication to generic abiraterone; **OR**
 - b. Enzalutamide (Xtandi) will be used in combination with talazoparib (Talzenna); **AND**
 - i. Documentation of deleterious (pathogenic) or suspected deleterious (likely pathogenic) alteration in BRCA1 or BRCA2 gene; **AND**
 - 1. Documentation of intolerance or contraindication to generic abiraterone in combination with olaparib (Lynparza); **OR**
 - ii. The member has an alteration in an HRR gene that is not BRCA1 or BCRA2 (e.g., *ATM*, *ATR*, *CDK12*, etc.); **OR**
 - 4. **Metastatic castration sensitive or castration naïve prostate cancer; AND**
 - i. **For generic abiraterone:**
 - a. The member has at least TWO of the following risk factors:
 - i. Gleason Score ≥ 7 (Grade Group ≥ 2)
 - ii. Bone lesions
 - iii. Presence of measurable visceral metastases; **AND**
 - b. Abiraterone will be used in combination with prednisone; **AND**
 - i. If used in combination with docetaxel, the provider attests that the member has high-volume metastatic burden; **AND**
 - c. The request is for generic abiraterone 250 mg tablets; **OR**

- i. Documentation of clinical rationale why 250 mg tablets would not be an effective regimen (convenience of a larger tablet size does not meet medical necessity); **OR**
 - ii. **For BRAND abiraterone (Zytiga), apalutamide (Erleada), darolutamide (Nubeqa), or enzalutamide (Xtandi):**
 - a. The member has at least TWO of the following risk factors:
 - i. Gleason Score ≥ 7 (Grade Group ≥ 2)
 - ii. Bone lesions
 - iii. Presence of measurable visceral metastases; **AND**
 - b. The member must have had an inadequate response, intolerance, or contraindication to generic abiraterone (Note: if criteria is met for generic abiraterone, use of the 250 mg tablets will be required); **AND**
 - c. If the request is for abiraterone (Zytiga), it will be used in combination with prednisone; **AND**
 - i. If used in combination with docetaxel, the provider attests that the member has high-volume metastatic burden; **OR**
 - d. If the request is for darolutamide (Nubeqa), it will be used in combination with docetaxel
- II. Darolutamide (Nubeqa), apalutamide (Erleada), enzalutamide (Xtandi), and abiraterone (Zytiga, Yonsa) are considered investigational when used for all other conditions, including but not limited to:
 - A. Cushing's Syndrome
 - B. Breast cancer
 - C. Hepatocellular carcinoma
 - D. Fallopian tube, ovarian, or uterine cancer

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. The medication is prescribed by, or in consultation with, an oncologist or urologist; **AND**
- IV. Darolutamide (Nubeqa), apalutamide (Erleada), enzalutamide (Xtandi), or abiraterone (Zytiga, Yonsa) will not be used in combination with any other oncolytic medication with the exception of docetaxel for mCSPC or PARP inhibitors [i.e., olaparib (Lynparza) and talazoparib (Talzenna)] for mCRPC; **AND**
- V. The member has either had a bilateral orchiectomy OR ongoing hormone suppression (e.g., GnRH therapy) will be used concurrently; **AND**
- VI. The member has experienced a response to therapy (e.g., stabilization of disease, decrease in tumor size or tumor spread, lack of disease progression); **AND**
 - 1. **Non-metastatic castration resistant prostate cancer;**

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- i. The request is for one of the following: darolutamide (Nubeqa), apalutamide (Erleada), OR enzalutamide (Xtandi); **OR**
- 2. **Non-metastatic castration sensitive prostate cancer; AND**
 - i. The request is for generic abiraterone 250 mg tablets and will be used in combination with prednisone, EBRT (unless contraindicated), and a GnRH analog; **OR**
 - ii. The request is for abiraterone 500mg tablets or brand abiraterone (Zytiga, Yonsa); **AND**
 - a. Documentation of clinical rationale why 250 mg tablets would not be an effective regimen (convenience of a larger tablet size does not meet medical necessity); **AND**
 - b. Treatment will be used in combination with EBRT (unless contraindicated), ADT, and prednisone; **OR**
- 3. **Metastatic castration resistant prostate cancer;**
 - i. The request is for generic abiraterone 250 mg tablets and will be used in combination with prednisone; **OR**
 - ii. The request is for generic abiraterone 500 mg tablets; **AND**
 - a. Documentation of clinical rationale why 250 mg tablets would not be an effective regimen (convenience of a larger tablet size does not meet medical necessity); **OR**
 - iii. The request is for brand abiraterone (Zytiga) plus prednisone OR brand abiraterone (Yonsa) plus methylprednisolone; **AND**
 - a. The member has an intolerance or contraindication to generic abiraterone (use of 250 mg tablets required); **OR**
 - iv. The request is for enzalutamide (Xtandi); **OR**
- 4. **Metastatic castration sensitive prostate cancer;**
 - i. The request is for generic abiraterone 250 mg tablets and will be used in combination with prednisone; **OR**
 - a. Documentation of clinical rationale why 250 mg tablets would not be an effective regimen (convenience of a larger tablet size does not meet medical necessity); **OR**
 - ii. The request is for enzalutamide (Xtandi), darolutamide (Nubeqa), or apalutamide (Erleada); **OR**
 - iii. The request is for brand abiraterone (Zytiga); **AND**
 - a. The member has had inadequate response, intolerance, or contraindication to generic abiraterone (use of 250 mg tablets required); **AND**
 - b. Will be used in combination with prednisone

Supporting Evidence

- I. Prostate cancer therapies have been evaluated for safety and efficacy in adults. There are multiple treatment modalities with the direction of therapy depending on the manifestations of the disease. The initial and continued approach should be directed by a specialist due to the

nuances of treatment, monitoring of disease, treatment safety, evaluation of efficacy, and consideration for patient specific goals.

- II. Many treatment options exist, and initial and further line therapy are contingent upon patient specific characteristics. These options include, but are not limited to, radiation therapy, prostatectomy, androgen deprivation pharmacotherapy, bilateral orchiectomy, chemotherapy, abiraterone (Zytiga, Yonsa), or androgen receptor inhibitors (e.g., enzalutamide (Xtandi), darolutamide (Nubeqa), apalutamide (Erleada)). Multi-modal therapy, such as abiraterone or enzalutamide with ADT, is commonly utilized; however, abiraterone and/or androgen receptor inhibitor combinations have not been evaluated for safety and efficacy to date. Continuation of ADT is commonly employed and is recommended as concomitant therapy as discontinuation of GnRH agonists are likely to result in an increase in serum testosterone and disease progression.
- III. Use of androgen receptor inhibitor (e.g., darolutamide [Nubeqa], apalutamide [Erleada], enzalutamide [Xtandi]) therapy after disease progression on abiraterone, or vice versa (i.e., abiraterone/androgen receptor inhibitor crossover therapy), has not yet been evaluated for safety and efficacy in quality clinical trials. One retrospective trial evaluating enzalutamide after treatment with abiraterone showed that very few patients (10% or less) had a significant decrease in PSA with enzalutamide therapy. A retrospective case series showed a similar lack of efficacy in regard to abiraterone after enzalutamide (Xtandi). Additionally, there are studies to suggest cross resistance in switching between second generation anti-androgens. It has been demonstrated that there is a cross-resistance mechanism between darolutamide, apalutamide, enzalutamide, and abiraterone. NCCN guidelines note evidence-based guidance on the sequencing of ADT agents remains limited.
- IV. **Non-metastatic castration resistant prostate cancer:** darolutamide (Nubeqa), apalutamide (Erleada), and enzalutamide (Xtandi) are the androgen receptor inhibitors that have been evaluated in this stage of disease. Concurrent treatment with steroids is not required. Patients in the trials for each of these medications had a prostate-specific antigen doubling time of 10 months or less and received GnRH therapy concurrently. Each therapy was evaluated in a double-blind, placebo-controlled trial.
 - Darolutamide (Nubeqa) was evaluated in the ARAMIS TRIAL. The primary outcome, metastasis free survival (MFS), showed a statistical significance over placebo (40 vs 18 months, $p < 0.001$). Apalutamide (Erleada) was evaluated in the SPARTAN trial, MFS was statistically significant compared to placebo (40 vs 16 months), and enzalutamide (Xtandi) was evaluated in the PROSPER trial. The MFS was significant compared to placebo (37 months vs 15 months).
 - Darolutamide (Nubeqa) does not cross the blood brain barrier; thus, may offer an improved safety profile compared to enzalutamide and even apalutamide (Erleada). There were low rates of fatigue, falls, fractures, and seizures; however, head-to-head trials have not yet been conducted and caution should be used when comparing across trials to make treatment decisions.
- V. **Non-metastatic castration sensitive prostate cancer:** abiraterone in combination with androgen deprivation therapy (ADT) (e.g. GnRH analogs) and prednisone, was evaluated in a phase III, randomized, open-label study (STAMPEDE) with 1974 participants with high-risk, non-metastatic prostate cancer. Participants were considered high risk if they are node positive alone, if they are node negative with two factors (stage T3 or T4, Gleason Score >8 , or PSA >40), or if there

was disease progression on ADT (defined by a PSA $\geq$ 4ng/mL with a doubling time of <6 months, or PSA $\geq$ 20 ng/mL). Radiotherapy was required for those participants with node negative and highly encouraged for those that were node positive. A total of 99% of participants with node negative and 77% of participants with node positive disease received radiotherapy (overall 85%). The primary outcome of metastasis-free survival (MFS) was significantly longer in the combination-therapy group versus ADT alone and 6-year MFS improved from 69% in the ADT groups to 82% in the combination therapy groups (HR 0.53, 95% CI 0.44–0.64; $p<0.0001$). There was a total of 147 deaths in the combination group compared to 236 in the ADT group – overall survival was significantly longer in the combination group vs ADT (not reached, 103–NE; HR 0.60, 95% CI 0.48–0.73, $p<0.0001$). Prostate-cancer-specific survival was significantly improved in the combination- therapy groups versus ADT alone (HR 0.49, 95% CI 0.37–0.65, $p<0.0001$). The most common ADE in combination group versus ADT was hypertension (393 (41%) vs 153 (5%)), aminotransaminases (332 (34%) vs 136 (14%)).

- VI. Enzalutamide (Xtandi) received FDA approval for treatment of non-metastatic, castration sensitive prostate cancer, with or without GnRH analog. Enzalutamide in combination with leuprolide, enzalutamide monotherapy and placebo plus leuprolide, was evaluated in a Phase III, randomized, double-blinded, study (EMBARK) with 1068 participants with high-risk, non-metastatic prostate cancer. Participants were considered high risk if they are node positive or had a PSA doubling time less than 9 months after EBRT. The primary outcome of metastasis-free survival (MFS) between the combination group vs leuprolide alone was evaluated. MFS was significantly longer in the combination-therapy group versus placebo and leuprolide (HR 0.42, 95% CI, 0.30-0.61, $p<0.0001$). The 5-year metastasis-free survival was 87.3% (95% confidence interval [CI], 83.0 to 90.6) in the combination group and 71.4% (95% CI, 65.7 to 76.3) in the leuprolide-alone group. Secondary analysis also demonstrated that enzalutamide monotherapy was also superior to leuprolide alone in delaying metastasis or death (HR 0.63; 95% CI, 0.46-0.87, $P=0.005$). The most common adverse event leading to discontinuation was fatigue (in 12 patients [3.4%] in the combination group, 4 patients [1.1%] in the leuprolide-alone group, and 8 patients [2.3%] in the monotherapy group).
 - NCCN prostate cancer guidelines provide a category 2a recommendation for use of abiraterone acetate in combination with prednisone, EBRT, and ADT in those categorized as high or very high risk, and such combination is listed as the preferred treatment. As of January 2024, NCCN guidelines have not been updated to include enzalutamide (Xtandi)'s new indication.
 - Contraindications to EBRT include, but are not limited to preexisting anal fistula, inflammatory bowel disease (e.g. ulcerative colitis, diverticulitis, etc.), unacceptable operative risks or medically unsuitable for anesthesia, history of previous pelvic radiotherapy, and ataxia telangiectasia.
- VII. **Metastatic, castration resistant prostate cancer:** enzalutamide (Xtandi) and abiraterone (Zytiga, Yonsa) have been evaluated for safety and efficacy. Enzalutamide (Xtandi) versus placebo was evaluated in those that had previously been treated with chemotherapy and those that were chemotherapy naïve. Overall survival was prolonged in both settings. Abiraterone (Zytiga, Yonsa) plus prednisone has also shown prolonged survival in this setting in those that have been previously treated with chemotherapy and those chemotherapy naïve. Head-to-head trials have not been completed to provide insight to superior therapy between abiraterone (Zytiga, Yonsa)

and enzalutamide (Xtandi). Abiraterone (Zytiga, Yonsa) is indicated in combination with prednisone; however, enzalutamide has safety concerns including CNS toxicities and seizures. Additionally, abiraterone (Zytiga, Yonsa) has generic availability.

- The combination therapy of enzalutamide (Xtandi) and talazoparib (Talzenna) was evaluated in the TALAPRO-2 trial. Talazoparib (Talzenna) is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes. A total of 805 patients were randomized 1:1 to either receive talazoparib/enzalutamide or placebo/enzalutamide. They were further stratified by previous novel hormonal therapy/docetaxel and HRR gene-alteration status. The primary outcome was radiographic progression free survival (rPFS) assessed by blinded independent central review per RECIST 1.1 (soft tissue disease) and Prostate Cancer Clinical Trials Working Group 3 (bone disease). Treatment with talazoparib/enzalutamide resulted in a 37% lower risk of radiographic progression or death compared to placebo plus enzalutamide (HR 0.63; 95% CI 0.51–0.78; $p < 0.0001$). The most common adverse effects in the treatment group were anemia (66%), neutropenia (36%), and fatigue (34%).
- In a randomized, double-blind, Phase 3 clinical trial (PROpel), the efficacy, safety, and tolerability of olaparib (Lynparza) was assessed versus placebo when given in addition to abiraterone in men with metastatic castration-resistant prostate cancer (mCRPC), who had not received prior chemotherapy or novel hormonal agents (NHAs; e.g., enzalutamide, apalutamide, abiraterone) in the 1st-line metastatic setting. Previous therapy with docetaxel in the neoadjuvant or adjuvant setting, as well as first-generation antiandrogen agents (e.g., bicalutamide, nilutamide) were permitted; however, were not required as part of the inclusion criteria. The primary endpoint, radiographic progression-free survival (rPFS), and secondary endpoints included OS and time to first subsequent anticancer therapy or death. In a predefined interim analysis (as of July 2022), olaparib (Lynparza) in combination with abiraterone reduced the risk of disease progression or death by 34% versus abiraterone alone (based on a hazard ratio [HR] of 0.66; 95% confidence interval [CI] 0.54-0.81; $p < 0.0001$). Median rPFS was 24.8 months for olaparib (Lynparza) plus abiraterone versus 16.6 months for abiraterone alone.
- As of 9/2023, there are no head-to-head trials suggesting superiority of one PARP inhibitor/antiandrogen combination therapy over another. Both olaparib/abiraterone and talazoparib/enzalutamide are categorized as useful in certain circumstances with a Category 1 recommendation per NCCN guidelines. olaparib/abiraterone was FDA approved for this indication in patients harboring a *BRCAm*, while talazoparib/enzalutamide carries a broader FDA approval encompassing all *HRRm*. DNA repair anomalies known as homologous recombination repair gene mutations (*HRRm*) are identified in approximately 25% of patients with mCRPC. HRR gene mutations can consist of mutations in *ATM*, *ATR*, *BRCA1*, *BRCA2*, *CDK12*, *CHEK2*, *FANCA*, *MLH1*, *MRE11A*, *NBN*, *PALB2*, or *RAD51C*. Approximately 10-15% of patients with mCRPC have the *BRCA1/BRCA2* gene mutations. These mutations have been associated with more aggressive disease and poor patient outcomes.

- VIII. **Metastatic high-risk castration sensitive prostate cancer:** abiraterone (Zytiga, Yonsa) plus prednisone has been evaluated for safety and efficacy. High risk disease was defined as having at least two of the following three risk factors: Gleason score eight or greater, presence of three or more bone lesions, evidence of measurable visceral metastases. Overall survival over placebo was shown to be statistically significant for abiraterone (Zytiga, Yonsa).
- NCCN prostate cancer guidelines provide a category 1 recommendation for use of abiraterone acetate in combination with docetaxel and ADT in those with a high-volume metastatic burden who are candidates for chemotherapy. This is based on the findings from the PEACE-1 clinical trial, which evaluated the safety and efficacy of standard of care (SOC) therapy, defined as docetaxel and ADT, against SOC plus abiraterone acetate and prednisone. The co-primary endpoint consisted of radiographic progression free survival (rPFS) and overall survival (OS). The abiraterone group demonstrated statistically significant benefit in rPFS and OS with a hazard ratio (HR) was 0.50 (99.9% CI 0.34-0.71; $p < 0.0001$) and 0.75 (95.1% CI 0.59-0.95; $p = 0.017$), respectively. However, further analysis based on volume of metastatic burden revealed that OS was only statistically significant in the population with high-volume metastatic burden (HR 0.72 [95.1% CI 0.55-0.95]; $p = 0.019$) compared to low-volume metastatic burden (HR 0.83 [95.1% CI 0.50-1.39]; $p = 0.66$). According to NCCN, high-volume disease is differentiated from low-volume disease by visceral metastases and/or four or more bone metastases, with at least one metastasis beyond the pelvis vertebral column. While the addition of docetaxel to abiraterone acetate and ADT did increase overall incidence of adverse reactions, it did not increase the incidence of severe or fatal adverse events and the safety profile is largely the same. Docetaxel is intended to be used at the same time or within a few weeks of starting therapy with darolutamide or abiraterone. In mHSPC, docetaxel is dosed on every 3-week cycles for a total of 6 cycles; completion of docetaxel therapy should reasonably be able to occur within the initial approval period of 6 months.
- IX. Although both strengths (250 mg and 500 mg) of abiraterone (Zytiga) are available in generic formulations, the 500 mg tablet remains at a significantly higher cost (40x greater) than the 250 mg tablet. Thus, use of generic abiraterone 250 mg is required over abiraterone 500 mg tablet.
- X. Apalutamide (Erleada) was evaluated in the metastatic, castration sensitive prostate cancer setting in combination with ADT versus ADT alone. This was not specifically in high-risk disease; however, 93% of subjects had a Gleason Score of seven or greater, and all subjects had bone metastases. Fifty-five percent of subjects had bone only metastases, and the remaining had additional metastases. Primary outcomes were radiographic progression free survival, which were statistically and clinically significant favoring apalutamide (Erleada). Head-to-head trials against abiraterone (Zytiga) have not occurred in this setting; however, the safety profile of abiraterone is further established at this time.
- XI. Enzalutamide (Xtandi) was evaluated in metastatic, castration sensitive, prostate cancer in combination with ADT versus ADT alone. This study was not specifically in high-risk disease; however, the majority of subjects (> 67%) had a Gleason score of 8 or greater – nearly 85% had bone metastases or bone and other metastases. Progression-free survival was 19 months for placebo plus ADT and was not reached for enzalutamide (Xtandi). Radiographic progression was

experienced by 13.8% of those receiving enzalutamide (Xtandi) and 32.6% for placebo plus ADT. Head-to-head trials against abiraterone have not occurred in this setting; however, abiraterone provides a better value for the treatment of mCSPC at this time. Additionally, enzalutamide (Xtandi) was evaluated in a Phase III open-label trial in addition to ADT versus ADE alone in those that were castration naïve. The primary endpoint of OS was statistically significant in a group of 125 subjects (HR for death: 0.67, CI 0.52-0.86, p=0.002).

- XII. Darolutamide (Nubeqa) was evaluated in metastatic, castration sensitive, prostate cancer in combination with ADT and docetaxel versus ADT/docetaxel alone. This was not specifically in high-risk disease; however, the majority of subjects (>77%) had a Gleason score of 8 or greater – nearly 80% had bone metastases and all other subjects had visceral or non-regional lymph node metastases. The hazard ratio for death was 0.68 (95% CI, 0.57 – 0.80; p<0.001) with overall survival (OS) at four years reported as 62.7% in the darolutamide group compared to 50.4% in the placebo group, despite a high percentage of patients who received subsequent life-prolonging systemic therapies (primarily a different androgen-receptor pathway inhibitor) among those who entered the follow-up in the placebo group (374 of 495 patients (75.6%). The side effect profile of darolutamide (Nubeqa) was consistent with previous evaluation and a higher incidence of treatment related adverse events was higher during the period when patients received both docetaxel and darolutamide (Nubeqa), and progressively decreased thereafter.

Investigational or Not Medically Necessary Uses

- I. Therapies in this policy are being evaluated in other conditions; however, quality data indicating safety and efficacy in the following settings are not yet available:
- A. Cushing's Syndrome
 - B. Breast cancer
 - C. Hepatocellular carcinoma
 - D. Fallopian tube, ovarian, or uterine cancer

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

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Related Policies

Policy Name	Disease state
olaparib (Lynparza)	Prostate cancer, metastatic castration-resistant, homologous recombination repair (HRR) gene-mutated
talazoparib (Talzenna)	Prostate cancer, metastatic castration-resistant, homologous recombination repair (HRR) gene-mutated

Policy Implementation/Update:

Action and Summary of Changes	Date
Added new indication for Xtandi (enzalutamide) in non-metastatic, castration sensitive prostate cancer upon FDA approval in November 2023. Xtandi was added to existing criteria. Updated step through Lynparza/abiraterone for mCRPC to delineate between patients with BRCAm vs HRRm.	02/2024

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Addition of criteria for abiraterone off-label use in non-metastatic, castration sensitive prostate cancer given published meta-analysis, long-term overall survival data from the STAMPEDE trial, and updated NCCN prostate cancer guideline recommendation (category 2a). Addition of pathway to coverage for enzalutamide (Xtandi) in combination with talazoparib (Talzenna) for metastatic castration-resistant prostate cancer given new FDA approved indication. Addition of verbiage to address combination use of olaparib (Lynparza) with abiraterone for mCRPC. Added related policies table.	09/2023
Added 240 mg Erleada tablets to policy	02/2023
Addition of darolutamide (Nubeqa) for metastatic castration-sensitive prostate cancer given new FDA-approved indication; Addition of docetaxel in combination with abiraterone acetate for metastatic castration-sensitive prostate cancer with high volume metastatic burden based on category 1 NCCN recommendation; Changed name of policy to 'Second Generation Anti Androgen Agents'	10/2022
Require clinical rationale for use of generic abiraterone 500 mg instead of generic 250 mg	05/2022
Addition of Grade Group referenced with Gleason Score	05/2021
Additional of newly approved enzalutamide (Xtandi) 40 mg and 80 mg tablets	11/2020
Addition of enzalutamide (Xtandi) for castration sensitive prostate cancer given new FDA-approved indication. Removal of requirement upon renewal to change to generic abiraterone. Consolidation of requirements for agents in the setting of castration sensitive prostate cancer to streamline policy. Formatting updates	12/2019
Darolutamide (Nubeqa) new agent available, criteria converted to policy, and all agents combined into one policy. Requirement of generic abiraterone added unless contraindicated or not tolerated. Addition of use of GnRH therapy in metastatic castration sensitive disease included. Yonsa brand added. Erleada now FDA approved for castration sensitive disease.	08/2019
Generic abiraterone requirement added prior to use of branded 250 mg.	12/2018
Enzalutamide new indication of non-metastatic resistant prostate cancer added. Clinical notes added and appropriate routing through criteria.	08/2018
Apalutamide (Erleada) criteria created	04/2018
Abiraterone new indication of metastatic, high-risk castration sensitive prostate cancer added. LATITUDE trial information incorporated as well.	02/2018
Enzalutamide (Xtandi) criteria created	02/2013
Abiraterone (Zytiga) criteria created	09/2011

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP086

Split Fill Management*

Description

Selinexor (Xpovio) is an oral nuclear export inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
selinexor (Xpovio)	80 mg tablet twice weekly carton	Relapsed or refractory multiple myeloma (MM)	1 carton (32 tablets)/28 days
	100 mg tablet once weekly carton		1 carton (20 tablets)/28 days
	80 mg tablet once weekly carton		1 carton (16 tablets)/28 days
	60 mg tablet once weekly carton		1 carton (12 tablets)/28 days
	40 mg tablet once weekly carton		1 carton (8 tablets)/28 days
	60 mg tablet twice weekly carton	Relapsed or refractory diffuse large B-cell lymphoma (DLBCL)	1 carton (24 tablets)/28 days
	40 mg tablet twice weekly carton		1 carton (16 tablets)/28 days
selinexor (Xpovio) PAK	40mg, 50mg, 60mg, and 80mg 28-day PAK	Relapsed or refractory multiple myeloma (MM); Relapsed or refractory diffuse large B-cell lymphoma (DLBCL)	16 tablets/28 days

Initial Evaluation

- I. **Selinexor (Xpovio)** may be considered medically necessary when the following criteria are met:
 - A. Member is 18 years of age or older; **AND**
 - B. Medication is prescribed by, or in consultation with, a hematologist or oncologist; **AND**
 - C. Not used in combination with any other oncology therapy unless outlined below; **AND**
 - D. A diagnosis of **multiple myeloma** when **ONE** of the following are met:
 1. The provider attests to the following:
 - i. The member has received ONE, but no more than THREE previous therapies; **AND**

- a. Previous treatments included at least one of the following medications:
 - i. Bortezomib (Velcade)
 - ii. Carfilzomib (Kyprolis)
 - iii. Ixazomib (Ninlaro)
 - iv. Daratumumab (Darzalex)
 - v. Immunomodulatory agent (e.g., lenalidomide, pomalidomide); **AND**
 - b. Selinexor (Xpovio) will be used in combination with bortezomib (Velcade) AND dexamethasone; **OR**
 - ii. The member has received **FOUR** or more previous therapies; **AND**
 - a. Refractory to ALL of the following medications:
 - i. TWO proteasome inhibitors (e.g., bortezomib, carfilzomib)
 - ii. TWO immunomodulatory medications (e.g., lenalidomide, pomalidomide)
 - iii. An anti-CD38 monoclonal antibody (e.g., daratumumab); **AND**
 - b. Selinexor (Xpovio) will be used in combination with dexamethasone.
- II. Selinexor (Xpovio) is considered investigational when used for all other conditions, including but not limited to:
 - A. Multiple myeloma when given as part of a quadruplet (“quad”) regimen
 - B. Diffuse large B-cell lymphoma

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
- II. Medication is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
- III. Clinical documentation of response to treatment such as stabilization or improvement in disease or symptoms; **AND**
- IV. Provider attests to the following:
 - A. The member has received ONE, but no more than THREE previous therapies; **AND**
 - 1. Selinexor (Xpovio) will be used in combination with bortezomib (Velcade) AND dexamethasone; **OR**
 - B. The member has received **FOUR** or more previous therapies; **AND**
 - 1. Selinexor (Xpovio) will be used in combination with dexamethasone.

Supporting Evidence

- I. As of February 2021, selinexor (Xpovio) has three FDA-approved indications:
 - In combination with bortezomib and dexamethasone in adult patients with multiple myeloma who have received at least one prior therapy
 - In combination with dexamethasone in adult patients with multiple myeloma who have previously received at least four prior therapies and whose disease is refractory to at

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least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody (penta-refractory)

- Relapsed or refractory diffuse large B-cell lymphoma (DLBCL)

II. Multiple myeloma (MM)

- Selinexor (Xpovio) is indicated for use in two different multiple myeloma settings: (1) received at least one prior therapy (*BOSTON trial*) and (2) received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody (*STORM trial*).
- Selinexor (Xpovio) for treatment in the setting of penta-refractory MM was approved via the accelerated approval pathway, and continued approval was contingent upon verification and description of clinical benefit in confirmatory trials. Results from the BOSTON trial confirmed continued approval for use in the setting of penta-refractory MM.

- i. **STORM**: Phase 2, open-label trial of 79 patients in combination with dexamethasone only. No other oncolytic therapies were included in the drug regimen. Patients included were previously treated with glucocorticoids, an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 mAb and refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab.
 1. The primary endpoint was objective response rate (ORR), which occurred in 21%. Secondary outcomes included progression free survival (PFS) and overall survival (OS), which resulted in 2.3 and 9.3 months, respectively.
 2. The safety profile is as follows: Sixty percent of patients in the trial experienced grade 3-4 adverse events including thrombocytopenia, anemia, and neutropenia. Additionally, other serious adverse events occurred such as febrile neutropenia, serious infections, and fatal serious bleeding.
 3. Selinexor (Xpovio) has not been sufficiently studied in the penta-refractory setting with further clinical evaluation of safety and efficacy needed to confirm a net health benefit and place in therapy for this medication.
- ii. **BOSTON**: Phase 3, randomized, open-label trial of 402 patients in combination with bortezomib and dexamethasone (N= 195 SEL-BTZ-Dex) compared to a combination with bortezomib and dexamethasone only (N=207 BTZ-Dex). Patients included had received one to three previous different regimens for multiple myeloma. Patients who previously received proteasome inhibitors (mono- or combination therapy) were required to have had at least a partial response and at least a 6-month interval since their last proteasome inhibitor therapy, with no history of discontinuation of bortezomib due to Grade 3+ AEs.
 1. The primary efficacy endpoint was progression free survival (PFS), which was 13.93 months in the SEL-BTZ-Dex arm versus 9.46 months in the BTZ-Dex arm. Key secondary endpoints were overall survival (OS), which was not reached in the SEL-BTZ-Dex arm versus 25 months in the BTZ-Dex arm; overall response rate (ORR) of 76.4% in the SEL-BTZ-Dex arm versus 62.3% in the BTZ-Dex arm; duration of response (DoR) of 20.3 months in the SEL-BTZ-

Dex arm versus 12.9 months in the BTZ-Dex arm; time to response (TTR) of 1.1 months in the SEL-BTZ-Dex arm versus 1.4 months in the BTZ-Dex arm.

2. Safety results were analyzed in all patients who received at least one dose of the study drug (N=195 SEL-BTZ-Dex, N=204 BTZ-Dex). The most common adverse events ($\geq 20\%$ incidence) included thrombocytopenia, anemia, nausea, fatigue, decreased appetite, diarrhea, peripheral neuropathy, weight loss, asthenia, cataract, and vomiting. Selinexor (Xpovio) showed an 81% treatment discontinuation rate: 21% due to adverse events versus 16% in the BTZ-Dex arm.

- Recommended dosage for MM:
 - i. In combination with bortezomib and dexamethasone is selinexor (Xpovio) 100 mg taken orally once weekly on Day 1 of each week until disease progression or unacceptable toxicity.
 - ii. In combination with dexamethasone is selinexor (Xpovio) 80 mg taken orally on Days 1 and 3 of each week until disease progression or unacceptable toxicity.
- As of February 2021, the National Comprehensive Cancer Network (NCCN) treatment guideline for previously treated multiple myeloma has included selinexor (Xpovio) in combination with bortezomib and dexamethasone as “Other Recommended Regimens” (Category 1 recommendation). Additionally, NCCN recommends selinexor (Xpovio) in combination with dexamethasone as “Useful in Certain Circumstances” for patients with relapsed/refractory multiple myeloma who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody (Category 2A recommendation).

III. Diffuse large B-cell lymphoma (DLBCL)

- **SADAL**: Phase 2, an open-label, single-arm, multi-cohort trial of 127 patients with de novo DLBCL or DLBCL transformed from previously diagnosed indolent lymphoma, previously treated with two to five lines of therapy and progressed after, or were not candidates for autologous stem-cell transplantation were included. Previous systemic regimens permitted included at least one course of anthracycline-based chemotherapy (unless contraindicated due to cardiac dysfunction, in which case, other active drugs such as etoposide, bendamustine, or gemcitabine were given) and at least one course of anti-CD20 immunotherapy such as rituximab. Low dose dexamethasone (4 mg) was permitted as it does not show anti-lymphoma activity. FDA approval was based on the overall response rate (ORR).
 - i. The primary efficacy endpoint was overall response rate (ORR), which occurred in 28%, and the secondary endpoint was duration of response (DoR), which was 9.3 months. Based on analysis of this clinical trial data, quality of the evidence is considered low given the lack of comparator and open-label trial design, as well as, the lack of clinically meaningful outcomes in morbidity, mortality, and quality of life – medication efficacy has not yet been confirmed.

- ii. Safety results were analyzed in all patients who received at least one dose of selinexor (Xpovio) (N=125). The most common adverse events ($\geq 20\%$ incidence) included thrombocytopenia, nausea, fatigue, anemia, decreased appetite, diarrhea, constipation, neutropenia, weight loss, vomiting, pyrexia, and asthenia. There are no specific contraindications to selinexor (Xpovio); however, warnings and precautions include: thrombocytopenia, neutropenia, gastrointestinal toxicity, hyponatremia, serious infection, neurological toxicity, and embryo-fetal toxicity. Selinexor (Xpovio) showed a 93% treatment discontinuation rate: 63% due to disease progression, 10% withdrawal by patient, 7% death, 6% physician decision, and 7% due to adverse events.
- Selinexor (Xpovio) for treatment in the setting of DLBCL received accelerated approval from the FDA based on ORR and DoR. Continued approval for this drug may be contingent upon verification of clinical benefit in confirmatory trials. There is a Phase 2/3 trial underway to assess rituximab + gemcitabine + dexamethasone + platinum (R-GDP) with or without selinexor (Xpovio) in patients with relapsed/refractory diffuse large B-cell lymphoma.
- Recommended dosage for DLBCL:
 - i. Selinexor (Xpovio) 60 mg taken orally on Days 1 and 3 of each week until disease progression or unacceptable toxicity.
- As of February 2021, the National Comprehensive Cancer Network (NCCN) treatment guideline for B-cell lymphomas has included selinexor (Xpovio) as third-line and subsequent treatment with a Category 2A recommendation.

Investigational or Not Medically Necessary Uses

- I. Selinexor (Xpovio) has not been sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Quadruple (“quad”) regimen
 - i. Although triplet regimens remain the standard of care for multiple myeloma, there is growing interest in quad regimens which may include the addition of monoclonal antibodies (e.g., daratumumab [Darzalex], elotuzumab [Empliciti]) to standard triplet backbone regimens. The current evidence available to support this use is limited to case series or small trials. Larger studies evaluating the safety and efficacy of these regimens are underway.
 - B. Diffuse large B-cell lymphoma
 - i. Refer to SADAL trial information under Supporting Evidence

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

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Appendix

Table 1: Classification of Medications used for Multiple Myeloma

Proteasome Inhibitors	Immunomodulatory Agents	Monoclonal Antibodies	Histone Deacetylase Inhibitors	B-cell Maturation Antigen-Directed Antibody	Chemotherapy
- bortezomib - carfilzomib - ixazomib	- thalidomide - lenalidomide - pomalidomide	- elotuzumab - daratumumab - isatuximab-irfc	panobinostat	belantamab mafodotin-blmf	- cyclophosphamide - doxorubicin - cisplatin - etoposide - melfalan - bendamustine

Table 2: Selinexor (Xpovio) Dosage Reduction Steps for Adverse Reactions

	MM In combination with Bortezomib and Dexamethasone	MM In combination with Dexamethasone	DLBCL
Recommended Starting Dosage	100 mg once weekly	80 mg Days 1 and 3 of each week (160 mg total per week)	60 mg Days 1 and 3 of each week (120 mg total per week)
First Reduction	80 mg once weekly	100 mg once weekly	40 mg Days 1 and 3 of each week (80 mg total per week)
Second Reduction	60 mg once weekly	80 mg once weekly	60 mg once weekly
Third Reduction	40 mg once weekly	60 mg once weekly	40 mg once weekly
Fourth Reduction	Permanently discontinue	Permanently discontinue	Permanently discontinue

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10. National Comprehensive Cancer Network NCCN Guidelines: Multiple Myeloma 4.2021. December 2020. Available at https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf. Accessed February 2021.

Policy Implementation/Update:

Action and Summary of Changes	Date
Added Xpovio 28-day PAK to QL table	03/2025
Added split fill management, length of authorization. Updated quantity limits to include 40 mg tablet once weekly carton, as well as DLBCL dosage forms. Updated penta-refractory MM indication from E/I to allow criteria coverage. Added criteria coverage for new MM indication of at least one prior therapy. Added new DLBCL indication and quad-regimen for MM as E/I. Added additional supporting evidence to include more details surrounding all three indications. Added "Table 1: Classification of Medications used for Multiple Myeloma" and "Table 2: Selinexor (Xpovio) Dosage Reduction Steps for Adverse Reactions" under Appendix.	02/2021
Policy created	08/2019

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP193

Description

Selumetinib (Koselugo) and mirdametinib (Gomekli) are mitogen-activated protein kinase (MEK) inhibitors for both MEK 1 and 2 that inhibit the phosphorylation of extracellular signal related kinase (ERK) and reduce neurofibroma numbers, volume, and proliferation.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit*
selumetinib (Koselugo)	10 mg capsules	Pediatric patients ≥2 years of age with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable plexiform neurofibromas (PN)	120 capsules/30 days
	25 mg capsules		
mirdametinib (Gomekli)	1mg capsules	Adult and pediatric patients ≥2 years of age with neurofibromatosis type 1 (NF1) who have symptomatic plexiform neurofibromas (PN) not amenable to complete resection	42 capsules/28 days
	2mg capsules		42 capsules/28 days
	1mg tablet for oral suspension		84 tablets/28 days

*Please note that the dose is based on body surface area (BSA). Please see appendix for dosing limits. Quantity limit exceptions not allowed, except for dose reductions.

Initial Evaluation

- I. **Selumetinib (Koselugo) and mirdametinib (Gomekli)** may be considered medically necessary when the following criteria are met:
 - A. Medication is prescribed by, or in consultation with, a neurosurgeon, neurologist, or oncologist; **AND**
 - B. Documentation of member's weight and height; **OR**
 1. Documentation of member's body surface area (BSA); **AND**
 - C. Attestation member has undergone a baseline comprehensive ophthalmic assessment; **AND**
 - D. Attestation member has undergone a baseline assessment of left ventricular ejection fraction (LVEF); **AND**
 - E. Member has NOT experienced disease progression (increase in tumor size or tumor spread) while on a prior MEK inhibitor [e.g., selumetinib (Koselugo), mirdametinib (Gomekli), binimetinib (Mektovi), cobimetinib (Cotellic), trametinib (Mekinist), etc.]; **AND**
 - F. Member is between two and 17 years of age; **AND**
 1. Request is for selumetinib (Koselugo); **OR**
 2. Request is for mirdametinib (Gomekli); **AND**

- i. Treatment with selumetinib (Koselugo) has been contraindicated or not tolerated; **OR**
 - ii. Provider attests member is unable to swallow capsules; **OR**
- G. Member is 18 years of age or older and request is for mirdametinib (Gomekli); **AND**
- H. A diagnosis of **Neurofibromatosis type 1 (NF1)** when the following are met:
 - 1. Member has an inoperable plexiform neurofibromas (PN) or a PN that could not be completely surgically removed without risk for substantial morbidity (i.e., encasement or close proximity to vital structures, invasiveness, or high vascularity); **AND**
 - 2. Documentation member has symptoms that affect quality of life (e.g. pain, impaired physical function, compression of vital organs, respiratory impairment, visual dysfunction, and neurological dysfunction); **AND**
 - 3. Diagnosis confirmed by genetic testing; **OR**
 - i. Member meets at least two of the following criteria (a child of a parent with NF1 can be diagnosed if one or more of these criteria are met):
 - a. Six or more light brown spots (café-au-lait macules – CALMs) equal to, or greater than, 5 mm in longest diameter in prepubertal patients and 15 mm in longest diameter in post pubertal patient; **OR**
 - b. Freckling in the axillary or inguinal regions (Crowe sign); **OR**
 - c. Two or more neurofibromas of any type; **OR**
 - d. One plexiform neurofibroma; **OR**
 - e. Optic glioma (OPG); **OR**
 - f. Two or more iris hamartomas (Lisch nodules – dome-shaped gelatinous masses developing on the surface of the iris); **OR**
 - g. A distinctive osseous lesion, such as sphenoid wing dysplasia or long-bone dysplasia (with associated cortical thickening and medullary canal narrowing), with or without pseudoarthrosis; **OR**
 - h. A heterozygous pathogenic neurofibromin 1 (NF1) variant with a variant allele fraction of 50% in apparently normal tissue such as white blood cells
- II. Selumetinib (Koselugo) and/or mirdametinib (Gomekli) are considered investigational when used for all other conditions, including but not limited to:
 - A. Selumetinib (Koselugo) for the treatment of NF1-PNs in adults
 - B. Progressive or recurrent low grade glioma (LGG)
 - C. Langerhans cell histiocytosis (LCH) or other histiocytic disorders
 - D. Advanced or refractory solid tumors

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**

- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Member has exhibited response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread

Supporting Evidence

- I. Neurofibromatosis type 1 (NF1) is a rare autosomal dominant genetic disorder affecting 1 in every 3,000 to 4,000 people worldwide. Pathologic variants in the *NF1* gene cause errors in the creation of a protein, neurofibromin, which normally acts as a tumor suppressor. Neurofibromin is produced by many cells including oligodendrocytes and Schwann cells surrounding nerves. When mutated, tumors such as neurofibromas form along nerves throughout the body.
- II. Neurofibromatosis type 1 is characterized by café-au-lait macules, freckling in the axillary or inguinal region, Lisch nodules (iris hamartomas), and neurofibromas. Some people with neurofibromatosis type 1 develop plexiform neurofibromas or tumors that grow along nerves. These tumors, which usually develop in adolescence or adulthood, and are considered a major cause of morbidity and symptomatic plexiform neurofibromas often lead to disfigurement, pain, and functional impairment. Whole-body imaging reveals PNs in approximately 50 percent of patients with NF1. Plexiform neurofibromas may compress the airway or spinal cord and can transform into malignant peripheral nerve sheath tumors (MPNSTs). Surgery was previously considered primary therapy though it is now associated with tumor regrowth and increased morbidity.
- III. Neurofibromatosis type 1 is a multifaceted disease state. Both selumetinib (Koselugo) and mirdametinib (Gomekli) have complex dosing regimens and safety profiles; therefore, it should be prescribed by, or in consultation with, a neurologist or neurosurgeon for the treatment and management of NF1.
- IV. There is no published data from a head-to-head study between selumetinib (Koselugo), mirdametinib (Gomekli) and other MEK inhibitors [e.g., binimetinib (Mektovi®), cobimetinib (Cotellic®), trametinib (Mekinist®)] to show effectiveness for the treatment of pediatric patients two years of age and older with neurofibromatosis type 1 who have symptomatic, inoperable plexiform neurofibromas (PN). There is no data to show one MEK inhibitor could overcome common mechanisms of resistance of MEK inhibitors.
- V. Both selumetinib (Koselugo) and mirdametinib (Gomekli) are dosed on the basis of a member's body surface area (BSA). Current BSA and/or height and weight are required for dosing.
- VI. Per the revised diagnostic criteria for NF1 consensus recommendations, to establish a diagnosis of NF1, two of the following criteria have to be present. However, a child of a parent who meets the diagnostic criteria specified below merits a diagnosis of NF1 if one or more of the criteria are present:
 - Six or more café-au-lait macules over 5 mm in greatest diameter in prepubertal individuals and over 15 mm in greatest diameter in postpubertal individuals
 - Freckling in the axillary or inguinal region
 - Two or more neurofibromas of any type or one plexiform neurofibroma
 - Optic glioma (OPG).
 - Two or more iris Lisch nodules identified by slit lamp examination or two or more choroidal abnormalities (CAs)—defined as bright, patchy nodules imaged by optical coherence tomography (OCT)/near-infrared reflectance (NIR) imaging

- A distinctive osseous lesion such as sphenoid dysplasia, anterolateral bowing of the tibia, or pseudarthrosis of a long bone
 - A heterozygous pathogenic NF1 variant with a variant allele fraction of 50% in apparently normal tissue such as white blood cells
- VII. Neurofibromatosis type 1 genetic testing may be performed for purposes of diagnosis, but if a child fulfills diagnostic criteria for NF1, molecular genetic confirmation is usually unnecessary. Molecular diagnosis of NF1 is available based on DNA analysis for a pathogenic variant in the NF1 gene. Only 4 genotype-phenotype correlations have been established (deletion of the entire NF1 gene, specific 3-base deletion in exon 22, Amino acid substitution at codon 1809, some missense or splicing variants are associated with “spinal NF1,”).

Koselugo

- VIII. The safety and efficacy of selumetinib (Koselugo) in pediatric patients two years of age or older with NF1 who have inoperable PN was established in the SPRINT trial (a Phase II, open-label, single arm, multicenter clinical trial).
- IX. The safety and efficacy of selumetinib (Koselugo) was evaluated in patients with NF1 who have inoperable (defined as a PN that could not be completely removed without risk for substantial morbidity due to encasement of, or close proximity to, vital structures, invasiveness, or high vascularity of the PN) and symptomatic [defined as PNs that may located around the orbit, face, upper and lower limbs, back, thorax, abdomen, neck brachial plexus and/or lumbosacral plexus, which result in clinical symptoms such as disfigurement, motor dysfunction (weakness and restricted range of motion), pain, respiratory impairment, visual dysfunction, and neurological dysfunction] PNs.
- X. The majority of patients were white, male, and the median age was 10.2 years. Patients had a median number of three morbidities present at baseline, with 13 patients having four morbidities assigned to their target PN at baseline. Morbidities were defined as motor, bowel and/or bladder, orbital (vision), and airway dysfunction and other dysfunctions that included pain, swallowing, disfigurement, and sensory neuropathy. Twenty-one patients had progressive disease at baseline, 15 had non-progressive disease, and 14 had insufficient data at baseline. Overall, 39 (78.0%) patients had received prior treatment for PN and/or another NF1-related tumor, with most patients having either medical therapy or surgery, or both. The two most common PN-directed medical treatments received by these patients were interferons (including peginterferon) and imatinib. Eighteen patients had received a single medical therapy, and the remaining patients had received multiple successive medical therapies.
- XI. The primary efficacy outcome measure was overall response rate (ORR), or the percentage of patients with complete response (defined as disappearance of target PN), or confirmed partial response (defined as a reduction in PN volume at a subsequent tumor assessment of $\geq 20\%$ within three to six months). No patient had a complete response and 37/50 (74%) achieved a partial response. A total of 28/50 (56%) patients with PR had a durable response after 12 months. Although selumetinib (Koselugo) showed a statistically significant reduction in tumor volume, the quality of evidence is low due to the single arm study design, small sample size, and unknown correlation between the primary outcome measure and morbidity, mortality, or quality of life.
- XII. Cardiomyopathy, defined as a decrease in left ventricular ejection fraction (LVEF) of 10% or more below baseline, occurred in 23% of the 74 pediatric patients who received selumetinib (Koselugo) in the clinical trial. The safety and efficacy, of use in those with a history of impaired LVEF or a baseline ejection fraction that is below the institutional LLN, has not been established.
- XIII. Blurred vision, photophobia, cataracts, and ocular hypertension occurred in 15% of 74 pediatric patients receiving selumetinib (Koselugo). Blurred vision resulted in dose interruption in 2.7% of

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patients. Ocular toxicity was resolved in 82% of 11 patients. Comprehensive ophthalmic assessments prior to initiating, and at regular intervals during treatment, for new or worsening visual changes are recommended.

Gomekli

- XIV. Mirdametinib (Gomekli) was studied in an open-label, Phase IIb trial in 114 patients (58 adults and 56 pediatrics) with NF1-PN causing significant morbidity that cannot be completely surgically removed and amenable to volumetric MRI analysis. The median (range) age was 34 years (18-69) for adults and 10 years (2-17) for children. The median (range) target PN volume was 196 mL (1-3,457) in adults and 99 mL (5-3,630) in children. Thirty-one adults (53%) and 35 children (62%) had investigator determined progressive PN at baseline. The most common NF1-PN-related morbidities in both cohorts were pain (adults, 90%; children, 70%) and disfigurement or major deformity (adults, 52%; children, 50%).
- XV. The primary efficacy outcome was confirmed objective response rate (ORR) as interpreted by a blinded independent central review. Confirmed partial response was defined as the proportion of patients with a $\geq 20\%$ reduction of target PN volume from baseline on consecutive scans during the 24-cycle treatment phase. Key secondary endpoints also included duration of response and changed from baseline in patient reported and/or parent proxy-reported outcomes of worst tumor pain severity.
- XVI. No patient (adult or pediatric) had a complete response. Forty-one percent (24/58) of adults and 52% (29/56) pediatric patients achieved a partial response. The median duration of response has not been met at this time though reported duration of response (DOR) at 12 months is 88% (21/58) and 90% (26/56) for adult and pediatric patients respectively. The duration of response at 24 months is lower at 50% (12/58) and 48% (14/56) for adult and pediatric patients respectively.
- XVII. Amongst adult participants 59% (17 of 29), 50% (13 of 26), and 42% (17 of 40) achieved a clinically meaningful improvement in NRS-11, PII, and PedsQL Total Score at cycle 5 from baseline, respectively. Similarly for pediatric participants, clinically meaningful improvements were achieved in 57% (8 of 14) for patient-reported NRS-11, 33% (4 of 12) for patient-reported PII, 45% (5 of 11) for parent proxy-reported PII, 39% (14 of 36) for patient reported PedsQL Total Score, and 41% (17 of 41) for parent proxy-reported PedsQL Total Score.
- XVIII. The results of the ReNu clinical trial were able to demonstrate clinically significant response rates in both adult and pediatric populations. Additionally, patient reported outcomes were able to assess changes in worst tumor pain severity with meaningful improvement being seen across multiple scoring tools. However, the design of the clinical trial leaves some questions to validity. Open label trial design paired with a lack of concealment and randomization leads to concerns regarding confirmation bias for patient reported outcomes. Though bias regarding treatment effect in ORR measures would be mitigated with a blinded independent central review. The overall response rate is being driven entirely by partial response in both the adult and pediatric cohorts. It is undetermined if partial response leads to durable improvement in the overall course of disease and improved survival or if therapy correlates to a reduction in the risk of developing MPNSTs. Long term safety and the potential benefits of extended therapy with mirdametinib (Gomekli) remains unclear. Therefore, the overall confidence in a substantial benefit is considered low but the data may be sufficient to make healthcare decisions.
- XIX. The most common treatment emergent adverse events (TEAEs) reported for mirdametinib (Gomekli) included dermatitis acneiform (78% vs 43%), diarrhea (48% vs 38%), nausea (36% vs 21%), vomiting (28% vs 14%), fatigue (21% vs 9%), decreased injection fraction (12% vs 20%), increased blood creatinine phosphokinase (10% vs 20%), and paronychia (2% vs 30%) in adult and pediatric patients respectively. Warnings and precautions include ocular toxicity, left

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ventricular dysfunction, dermatologic adverse reaction, and embryo-fetal toxicity. Two patients reported retinal vein occlusion on study drug. At the last follow-up one patient's visual acuity remains impaired from baseline while the second individual had resolution without dose modification. Adults (31%) experienced a dose interruption, 10 (17%) underwent dose reduction, and 13 (22%) discontinued treatment because of AEs. Seventeen children (30%) had a dose interruption, seven (12%) underwent a dose reduction, and five (9%) discontinued treatment because of AEs.

- XX. The FDA label for mirdametininb (Gomekli) recommends conducting comprehensive ophthalmic assessments prior to initiating therapy and at regular intervals during treatment and for new or worsening visual changes or blurred vision. Continue, withhold, reduce the dose, or permanently discontinue therapy based on severity. Similarly, recommendation is to assess ejection fraction by echocardiogram prior to initiating therapy and every 3 months during the first year, then as clinically indicated thereafter. Withhold, reduce the dose, or permanently discontinue based on severity.

Investigational or Not Medically Necessary Uses

- I. Selumetinib (Koselugo) and/or mirdametininb (Gomekli) have not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Selumetinib (Koselugo) for the treatment of NF1-PNs in adults
 - a. Selumetinib (Koselugo) is currently under investigation for the treatment of NF1-PNs in an adult population in the Phase III randomized, double-blind, placebo-controlled KOMET trial. The primary endpoint is confirmed ORR by cycle 16 as assessed by ICR. ORR is defined as the percentage of patients with confirmed complete response (disappearance of PNs) or partial response (at least 20% reduction in tumour volume). As of May 2025, selumetinib (Koselugo) has not been approved by the FDA and further information regarding potential regulatory approval is limited.
 - B. Progressive or recurrent low grade glioma (LGG)
 - C. Langerhans cell histiocytosis (LCH) or other histiocytic disorders
 - D. Advanced or refractory solid tumors

Appendix

Table 1: Recommended Dosage for selumetinib (Koselugo) Based on Body Surface Area

Body Surface Area (m ²)	Recommended Dosage	Quantity Level Limit
0.55 – 0.69	20 mg in the morning and 10 mg in the evening	90 capsules/30 days
0.70 – 0.89	20 mg twice daily	120 capsules/30 days
0.90 – 1.09	25 mg twice daily	60 capsules/30 days
1.10 – 1.29	30 mg twice daily	180 capsules/30 days
1.30 – 1.49	35 mg twice daily	120 capsules/30 days
1.50 – 1.69	40 mg twice daily	240 capsules/ 30 days
1.70 – 1.89	45 mg twice daily	180 capsules/30 days
≥ 1.90	50 mg twice daily	120 capsules/30 days

Table 2: Recommended Dosage for mirdametininb (Gomekli) Based on Body Surface Area

Body Surface Area (m ²)	Recommended Dosage for Capsules or Tablets for Oral Suspension	Quantity Level Limit	
		Capsules	Tablets for Suspension
0.40 to 0.69	1 mg twice daily	42 capsules/28 days	42 tablets/28 days
0.70 to 1.04	2 mg twice daily	42 capsules/28 days	84 tablets/28 days
1.05 to 1.49	3 mg twice daily	126 capsules/28 days	126 tablets/28 days
≥ 1.50	4 mg twice daily	84 capsules/28 days	168 tablets/28 days

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
encorafenib (Braftovi®), binimetinib (Mektovi®)	Malignant melanoma, unresectable or metastatic, with BRAF V600E or V600K mutation, combination therapy
	Metastatic colorectal cancer, with BRAF V600E mutation, combination therapy
trametinib (Mekinist®), dabrafenib (Tafinlar®)	Anaplastic thyroid carcinoma, advanced or metastatic, BRAF V600E mutated, combination therapy
	Melanoma, adjuvant therapy for malignant disease, BRAF V600E or K mutated, combination therapy, or monotherapy in treatment naïve patients
	Non-small cell lung cancer, metastatic, BRAF V600E mutated, combination therapy

	Unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options
	Pediatric low-grade glioma (LGG) with a BRAF V600E mutation, combination therapy
cobimetinib (Cotellic)	Unresectable or metastatic melanoma with a BRAF V600E or V600K mutation
vemurafenib (Zelboraf)	Unresectable or metastatic melanoma with a BRAF V600E mutation
	Erdheim-Chester Disease with a BRAF V600E mutation

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated policy to include mirdametinib (Gomekli) for the treatment of NF1-PNs. Updated to build out E/I indications. Updated supporting evidence to include mirdametinib (Gomekli) and background information on the disease state and diagnostic criteria. Added additional information regarding the selumetinib (Koselugo) clinical trials. Added related policies table.	08/2025
Policy created	08/2020

Policy Type: PA

Pharmacy Coverage Policy: UMP309

Description

Semaglutide (Wegovy) is a subcutaneously administered glucagon-like peptide (GLP-1) receptor antagonist.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
semaglutide (Wegovy)	Major adverse cardiovascular events (MACE) risk reduction in adults with established cardiovascular disease and obesity or overweight	0.25 mg/0.5 mL	2 mL/28 days
		0.5 mg/0.5 mL	
		1 mg/0.5 mL	
	Excess body weight and weight maintenance in patients 12 years and older with obesity and adults with overweight*	1.7 mg/0.75 mL	3 mL/28 days
		2.4 mg/0.75 mL	
	Nonalcoholic steatohepatitis (NASH)/ Metabolic Dysfunction-Associated Steatohepatitis (MASH)		

*Treatment for weight loss falls in a category of medications that are not covered under the prescription benefit. Drugs used for weight loss are excluded from coverage. Please refer to the member handbook/certificate of coverage for further information.

Initial Evaluation

- I. **Semaglutide (Wegovy)** may be considered medically necessary when the following criteria are met:
 - A. Member is 18 years of age or older; **AND**
 - B. The request is for **Major Adverse Cardiovascular Events (MACE) risk reduction**; **AND**
 1. Chart note documentation of established cardiovascular disease defined by one of the following:
 - i. Prior myocardial infarction
 - ii. Prior stroke (ischemic or hemorrhagic)
 - iii. Symptomatic carotid artery disease as confirmed by one or more of the following:
 - a. Moderate to severe carotid artery stenosis (occlusion > 50%)
 - b. Revascularization of the internal carotid artery
 - c. One or more transient ischemic attacks with focal neurological dysfunction or transient monocular blindness

- iv. Symptomatic coronary artery disease as confirmed by one or more of the following:
 - a. Coronary stenosis $\geq 50\%$
 - b. Symptomatic Angina Pectoris
 - c. Prior coronary revascularization
- v. Symptomatic peripheral arterial disease (PAD), as confirmed by one or more of the following:
 - a. Intermittent claudication with ankle-brachial index (ABI) <0.85 (at rest)
 - b. Peripheral arterial revascularization procedure
 - c. Amputation due to atherosclerotic disease; **AND**
- 2. Member's body mass index (BMI) is $\geq 27 \text{ kg/m}^2$ within the last three months; **AND**
- 3. Member does not have type 1 or type 2 diabetes; **AND**
- 4. Member does not have NYHA Class IV heart failure; **AND**
- 5. Provider attestation that medication is used in combination with a reduced calorie diet and increased physical activity; **AND**
- 6. Member does not currently use any tobacco products (e.g., cigarettes, chewing tobacco); **OR**
 - i. The member is being managed for tobacco cessation; **AND**
- 7. Documentation that member is optimizing all of the following standard of care pharmacologic treatments, unless ineffective, not tolerated, not indicated, or all are contraindicated:
 - i. Antihypertensive therapy (e.g., ACE inhibitor [e.g., lisinopril, ramipril], ARB [e.g., losartan, valsartan], beta-blocker [e.g., metoprolol, carvedilol])
 - ii. Lipid lowering therapy (e.g., statins [atorvastatin, simvastatin], ezetimibe)
 - iii. Antiplatelet therapy (e.g., aspirin, clopidogrel, ticagrelor); **OR**
- C. The request is for **nonalcoholic steatohepatitis (NASH)/ Metabolic Dysfunction-Associated Steatohepatitis (MASH); AND**
 - 1. Medication is prescribed by, or in consultation with, a hepatologist or gastroenterologist; **AND**
 - 2. Diagnosis is biopsy confirmed; **OR**
 - i. Diagnosis is confirmed by a fibrosis-4 index (FIB-4) score of more than 1.3 and less than 3.48 and ONE of the following:
 - a. Fibroscan score $> 8 \text{ kPa}$
 - b. Enhanced liver fibrosis (ELF) score ≥ 9.8
 - c. Magnetic resonance elastography (MRE) score $> 3.2 \text{ kPa}$; **AND**
 - 3. Documented liver fibrosis stage F2 or F3; **AND**
 - 4. Other causes of liver disease or hepatic steatosis have been ruled out (e.g., alcoholic steatohepatitis, acute fatty liver, autoimmune hepatitis, Hepatitis A, B or C, hemochromatosis, drug-induced liver disease, etc.); **AND**
 - 5. Member has ONE of the following comorbidities:
 - i. Overweight or Obesity (BMI $\geq 25 \text{ kg/m}^2$)

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- ii. Hypertension
 - iii. Dyslipidemia
 - iv. Pre-diabetes
 - v. Type 2 Diabetes Mellitus; **AND**
 - 6. Provider attestation member has adopted liver-protective lifestyle interventions such as optimizing weight loss, dietary changes, and exercise; **AND**
 - 7. Provider attestation member is optimizing standard of care pharmacologic treatment to manage comorbid diseases, including, but not limited to cardiovascular disease, dyslipidemia, diabetes, hypertension; **AND**
 - 8. Member does not have evidence of cirrhosis, hepatic decompensation, or hepatocellular carcinoma (HCC)
- II. Semaglutide (Wegovy) is considered not medically necessary when criteria above are not met and/or when used for:
- A. Major Adverse Cardiovascular Events (MACE) risk reduction in patients with type 2 diabetes mellitus and overweight or obesity
- III. Semaglutide (Wegovy) is considered investigational when used for all other conditions, including but not limited to:
- A. Major Adverse Cardiovascular Events (MACE) risk reduction in patients without prior myocardial infarction, prior stroke, or established symptomatic peripheral artery disease (PAD)
 - B. Major Adverse Cardiovascular Events (MACE) risk reduction in patients with NYHA stage IV heart failure
 - C. Heart failure symptom reduction in patients with overweight or obesity
 - D. Evidence of cirrhosis (F4), hepatic decompensation, or hepatocellular carcinoma (HCC)

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. The request is for **Major Adverse Cardiovascular Events (MACE) risk reduction; AND**
 - A. Chart note documentation of established cardiovascular disease defined by one of the following:
 - 1. Prior myocardial infarction
 - 2. Prior stroke (ischemic or hemorrhagic)
 - 3. Symptomatic carotid artery disease as confirmed by ≥ 1 of the following:
 - i. Moderate to severe carotid artery stenosis (occlusion > 50%)
 - ii. Revascularization of the internal carotid artery
 - iii. One or more transient ischemic attacks with focal neurological dysfunction or transient monocular blindness

4. Symptomatic coronary artery disease as confirmed by ≥ 1 of the following:
 - i. Coronary stenosis $\geq 50\%$
 - ii. Symptomatic Angina Pectoris
 - iii. Prior coronary revascularization
5. Symptomatic peripheral arterial disease (PAD), as evidenced by ≥ 1 of the following:
 - i. Intermittent claudication with ankle-brachial index (ABI) < 0.85 (at rest)
 - ii. Peripheral arterial revascularization procedure
 - iii. Amputation due to atherosclerotic disease; **AND**
- B. Member does not have type 1 or type 2 diabetes; **AND**
- C. Member does not have NYHA Class IV heart failure; **AND**
- D. Provider attestation that medication is used in combination with a reduced calorie diet and increased physical activity; **AND**
- E. Member does not currently use any tobacco products (e.g., cigarettes, chewing tobacco); **OR**
 1. The member is being managed for tobacco cessation; **AND**
- F. Documentation that member is optimizing all of the following standard of care pharmacologic treatments, unless ineffective, not tolerated, not indicated, or all are contraindicated:
 1. Antihypertensive therapy (e.g., ACE inhibitor [e.g., lisinopril, ramipril], ARB [e.g., losartan, valsartan], beta-blocker [e.g., metoprolol, carvedilol])
 2. Lipid lowering therapy (e.g., statins [atorvastatin, simvastatin], ezetimibe)
 3. Antiplatelet therapy (e.g., aspirin, clopidogrel, ticagrelor); **OR**
- IV. The request is for **nonalcoholic steatohepatitis (NASH)/ Metabolic Dysfunction-Associated Steatohepatitis (MASH); AND**
 - A. Disease response to treatment defined by improvement in fibrosis or stabilization/no worsening of fibrosis as determined by standardized testing (e.g., biopsy, transient elastography (e.g., FibroScan), magnetic resonance elastography (MRE), etc.); **AND**
 - B. Member has not progressed to cirrhosis, experienced hepatic decompensation events, or hepatocellular carcinoma (HCC)

Supporting Evidence

- I. Semaglutide (Wegovy) has not been studied in patients < 18 years of age for the indication of Major Adverse Cardiovascular Events (MACE) risk reduction in those affected by overweight or obesity or for the indication of non-alcoholic steatohepatitis (NASH)/ Metabolic Dysfunction-Associated Steatohepatitis (MASH), therefore, the net health benefit in a younger patient population has not been established at this time.

MACE risk reduction

- II. Semaglutide (Wegovy) for MACE risk reduction in patients with overweight or obesity was studied in one Phase 3, randomized, double-blind, placebo-controlled trial (SELECT). Patients were included if they were ≥ 45 years of age, had a body mass index (BMI) $\geq 27 \text{ kg/m}^2$, and had preexisting cardiovascular disease as evidenced by one of the following: prior myocardial infarction (MI), prior stroke (ischemic or hemorrhagic), or symptomatic peripheral arterial disease (PAD), as evidenced by intermittent claudication with ankle-brachial index (ABI) less

than 0.85 (at rest), peripheral arterial revascularization procedure, or amputation due to atherosclerotic disease. At baseline, the majority of patients had prior MI (68%), followed by stroke (18%), and symptomatic PAD (4%), and about 8% had two or more of these events. After a mean of 33 months of treatment, results demonstrated a 20% risk reduction (HR 0.80; 95% CI 0.72-0.90; $p < 0.001$) in the composite of death from cardiovascular causes, nonfatal MI, and nonfatal stroke in favor of semaglutide (Wegovy) vs placebo. Efficacy (i.e., MACE risk reduction) has not been established in patients without these major cardiovascular events at baseline, as such, use in primary prevention of MACE is considered experimental and investigational.

- III. Documentation of patient's body mass index (BMI) within the last three months is required to assess medical necessity for use. The safety and efficacy of semaglutide (Wegovy) for MACE reduction has not been established in those with BMI $< 27 \text{ mg/kg}^2$.
- IV. Semaglutide (Wegovy) has not been adequately studied in patients with diabetes and overweight or obesity and established cardiovascular disease for MACE risk reduction. The pivotal study (SELECT) excluded patients with type 1 and type 2 diabetes (history of gestational diabetes was allowed). Patients affected by diabetes type 2 or those that develop diabetes type 2 while on treatment with semaglutide (Wegovy) may benefit from treatment with anti-diabetic medications with established cardioprotective benefits in patients with diabetes (e.g., semaglutide [Ozempic]).
- V. Semaglutide (Wegovy) has not been adequately studied in patients with NYHA Class IV heart failure symptoms for MACE risk reduction. The pivotal trial (SELECT) excluded patients with NYHA Class IV heart failure symptoms. Semaglutide (Wegovy) has been studied in a smaller subset of patients with NYHA Class IV heart failure with obesity in a different trial called STEP-HFpEF which showed improved heart failure symptoms in those taking semaglutide (Wegovy), however, MACE outcomes were not evaluated. As such, efficacy of semaglutide (Wegovy) in patients with NYHA Class IV HF for risk reduction of MACE has not been established and use in this population is considered experimental and investigational at this time.
- VI. For MACE risk reduction, semaglutide (Wegovy) has been evaluated on top of standard of care which includes healthy lifestyle guidance (recommendations on improved diet and physical activity, tobacco cessation) and standard of care pharmacologic therapy for cardiovascular disease (e.g., post-MI, post-stroke, PAD therapies). Overweight and obesity are major risk factors for development of future CV events, as such, first-line therapies for overweight and obesity which includes lifestyle counseling should be maximized. Tobacco use is an additional risk factor for development of CV events; therefore, concurrent tobacco use is not allowed unless patients are actively undergoing tobacco cessation. Additionally, SELECT trial studied semaglutide (Wegovy) in combination with drugs that treat or prevent CV disease (e.g., anti-hypertensives, lipid-lowering agents, anticoagulants, aspirin), for maximal benefit, standard of care agents for CVD should be optimized.

NASH/MASH

- VII. Non-alcoholic fatty liver disease (NAFLD) is characterized by an abnormal accumulation of fat in the liver. NAFLD can be subcategorized as nonalcoholic fatty liver (NAFL), in which there is hepatic steatosis (HS) but no injury to liver cells, and as nonalcoholic steatohepatitis (NASH), in which HS is accompanied by hepatocellular injury.
- VIII. NASH can progress to liver fibrosis, and liver fibrosis can progress to irreversible cirrhosis and hepatocellular carcinoma (HCC). NASH and alcoholism are the top two indications for liver

transplantations and is the leading indication for liver transplantation in adults 65 years of age and older and women of all ages. NAFLD is closely linked to and often precedes the development of metabolic abnormalities (insulin resistance, dyslipidemia, obesity, and hypertension). Having several metabolic abnormalities confers an even greater risk of histological progression of NASH and all-cause mortality.

- IX. In 2023, it was proposed by hepatology medical societies that the naming for these conditions be updated to metabolic-associated fatty liver disease (MAFLD) and metabolic steatohepatitis (MASH).
- X. Diagnosis of suspected disease in most patients is based on clinical and laboratory data as well as imaging with appropriate exclusion of other liver conditions, but NASH is also a diagnosis of exclusion, which includes excluding: other causes of hepatic steatosis [alcoholic steatohepatitis, acute fatty liver, autoimmune hepatitis, Hepatitis A, B and C, hemochromatosis, drug-induced liver disease, etc.), absence of coexisting chronic liver disease, and exclusion of significant alcohol consumption.
- XI. Abnormal laboratory results indicating liver injury (e.g., aminotransferase levels (AST, ALT, etc.) may be detected and managed by primary care practitioners (PCPs) but should not be used in isolation to make a definitive NASH diagnosis. Individuals with intermediate to high-risk NASH or cirrhosis should be referred to hepatology or gastroenterology to undergo additional monitoring and confirmatory tests.
- XII. Liver biopsy is regarded as the gold standard to diagnose NASH. Several noninvasive testing (NIT) methods to detect fibrosis in patients with liver disease have been established as alternatives to biopsy, however, may not provide accurate diagnostic specificity. Initial risk assessment begins with evaluation of risk of advanced fibrosis (fibrosis-4 index (FIB-4) tool). The FIB-4 tool is a blood-based calculation that estimates liver fibrosis. Those who may have a moderate or high risk of advanced disease based on FIB-4 (≥ 1.3 and < 3.48) should undergo secondary risk assessment such as transient elastography (TE) (e.g., Fibroscan), magnetic resonance elastography (MRE), and the enhanced liver fibrosis (ELF) test. A Fibroscan score of > 8 and MRE score > 3.2 kPa are suggestive of moderate to advanced fibrosis. The ELF test is used as prognostication and recommended as a secondary risk assessment, particularly when availability of elastography may be limited. An ELF score ≥ 9.8 indicates intermediate risk of fibrosis and disease progression to cirrhosis. Although standard ultrasound can detect hepatic steatosis, it is not recommended as a tool to identify hepatic steatosis due to low sensitivity across the NAFLD spectrum. Patients with advanced fibrosis require further assessment and additional MRI-based tools can be used to further risk stratify patients. When there is diagnostic uncertainty in patients with indeterminate, unreliable, or conflicting NITs, diagnosis via liver biopsy remains the most reliable method to confirm advanced fibrosis and progression of NASH.
- XIII. Metabolic dysfunction-associated steatotic liver disease (MASLD) is defined by presence of liver steatosis and one metabolic risk factor (e.g., obesity, diabetes mellitus, dyslipidemia, hypertension). Patients with hepatic steatosis or clinically suspected NAFLD based on the presence of obesity and metabolic risk factors should undergo primary risk assessment with a fibrosis risk stratification by the fibrosis-4 (FIB-4 index), which is a common noninvasive test to help estimate the amount of scarring in the liver. The score calculates age, AST and ALT levels, and platelet count.

- XIV. The 2024 American Association for the Study of Liver Diseases (AASLD) and 2022 American Association of Clinical Endocrinology (AACE) guidelines provide guidance on the clinical care pathway for initial risk stratification and management of patients with NASH:
- Low risk of advanced fibrosis is defined as an FIB-4 score < 1.3 , LSM < 8.0 kPa by transient elastography (TE) or a liver biopsy fibrosis stage of F0–F1.
 - Intermediate/Indeterminate risk is defined as an FIB-4 score between ≥ 1.3 and 2.67 and/or an LSM between 8.0 and 12.0 kPa on TE, and in those patients who are unable or unwilling to obtain a liver biopsy.
 - High risk is defined as an FIB-4 score > 2.67 , LSM > 12.0 kPa by TE, or a liver biopsy that shows clinically significant liver fibrosis (F2–F4).
- XV. Lifestyle intervention is the key therapeutic intervention for patients with NAFLD. The American Association for the Study of Liver Diseases (AASLD) guidance on the management of NAFLD endorse dietary modification, increased physical activity, and weight loss. A weight loss of 5% to 10% of body weight can reverse hepatic steatosis and stabilize or diminish NASH in many patients, but this goal is frequently difficult to achieve. AASLD emphasizes optimizing glucose control for patients with diabetes, lipid-lowering therapy for patients with hyperlipidemia, and abstinence from alcohol for patients with clinically significant hepatic fibrosis.
- XVI. The goal of pharmacologic therapy for NASH is to slow the progress of, halt, or reverse fibrosis while patients are still pre-cirrhotic. Resmetirom (Rezdiffra) was the first FDA-approved therapy for NASH. Vitamin E and pioglitazone have been used historically and may improve the histologic changes of NASH, but data are limited. Some of the medications approved for commonly associated comorbidities such as T2DM and obesity have been studied in the context of NASH and may reduce liver enzymes or steatosis or improve liver histology. Therefore, medications with possible liver-related benefits should be optimized when managing comorbidities.
- XVII. The ESSENCE trial is an ongoing, two-part, randomized, double-blind, placebo-controlled, multicenter, Phase 3 study. Part 1 evaluated efficacy and safety of semaglutide 2.4mg subcutaneously once weekly compared to placebo in treatment of MASH. A total of 800 participants were randomized 2:1 (stratified by presence of type 2 diabetes and fibrosis stage 2 and 3) to receive semaglutide (N=534) or placebo (N=266). Participants included were 18 years of age or older, had a histological presence of steatohepatitis with fibrosis stage 2 or fibrosis stage 3 according to the NASH CRN classification, and a NAS of ≥ 4 , with a score of ≥ 1 in steatosis, lobular inflammation and hepatocyte ballooning. Participants with cirrhosis, other chronic liver disease (e.g. history of ascites, variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis or liver transplantation, etc), daily alcohol consumption of > 20 g, and on resmetirom (Rezdiffra) were excluded. Baseline characteristics were similar between both groups with a mean age 56 years, 57.1% Female, BMI 34.6 kg/m², 55% had type 2 diabetes mellitus (T2DM), all had at least one MASLD cardiometabolic criterion, 250 (31.3%) had fibrosis stage 2, and 550 (68.8%) had fibrosis stage 3, and mean HbA1c 6.5%.
- XVIII. The primary outcome was improvement in liver histology, which was split into two primary endpoints, resolution of steatohepatitis and no worsening of liver fibrosis and improvement in liver fibrosis and no worsening of steatohepatitis. ESSENCE is a well-designed clinical trial that demonstrated semaglutide 2.4mg weekly achieved resolution of steatohepatitis with no worsening of liver fibrosis compared to placebo (62.9% vs 34.1%. difference 28.9% ($P < 0.0001$)).

Those treated with semaglutide achieved improvements in fibrosis with no worsening of steatohepatitis compared to placebo (37.0% vs 22.5%, difference 14.5%, $P < 0.0001$). Although these are surrogate endpoints, previous analyses have shown that NASH severity, as quantified by NAS and fibrosis stage, is strongly correlated with liver-related mortality and transplant-free survival. Clinical complications of MASH take years to develop and the efficacy of semaglutide in prevention of cirrhosis and liver transplants is unknown and will be realized in the real-world setting.

- XIX. The overall incidence of adverse event (AE) was comparable between both treatment groups, with the most common AE being nausea (36.3% vs 13.2%), diarrhea (26.9% vs 12.2%), and constipation (22.3% vs 8.4%). Discontinuations owing to AEs were also not significantly increased with semaglutide vs placebo.
- XX. Data from the ESSENCE trial will be reinforced with completion of part 2. ESSENCE part 2 is an ongoing clinical program that will evaluate cirrhosis-free survival at week 240.

Investigational or Not Medically Necessary Uses

- I. Semaglutide (Wegovy) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Major Adverse Cardiovascular Events (MACE) risk reduction in patients with type 2 diabetes mellitus and overweight or obesity
 - i. For this indication, semaglutide (Wegovy) is considered not medically necessary over available anti-diabetic drugs with established MACE risk reduction outcomes (e.g., semaglutide (Ozempic)).
 - B. Major Adverse Cardiovascular Events (MACE) risk reduction in patients without prior myocardial infarction, prior stroke, or symptomatic peripheral artery disease (PAD)
 - i. Primary prevention of MACE in patients with cardiovascular risk factors or CVD other than prior MI, prior stroke, or symptomatic PAD has not been established and is considered experimental and investigational when the request is for semaglutide (Wegovy).
 - C. Major Adverse Cardiovascular Events (MACE) risk reduction in patients with NYHA stage IV heart failure
 - i. MACE risk reduction in patients with NYHA stage IV HF and overweight or obesity has not been adequately studied and is considered experimental or investigational when the request is for semaglutide (Wegovy).
 - D. Heart failure symptom reduction in patients with overweight or obesity
 - i. Semaglutide (Wegovy) is being studied in multiple trials (e.g., STEP HFpEF, STEP HFpEF DM) in patients with heart failure to evaluate its effects on heart failure symptoms. At this time, requests for this indication are considered experimental and investigational.
 - E. Cirrhosis, hepatic decompensation, or hepatocellular carcinoma (HCC)
 - i. Patients with cirrhosis, patients with prior hepatic decompensation events (e.g., variceal hemorrhage, ascites, hepatic encephalopathy), or in hepatocellular carcinoma (HCC) were excluded from participating in the ESSENCE clinical program. Reversal of cirrhosis in these patients may not be feasible and the

efficacy and safety of semaglutide (Wegovy) in this patient population is unknown.

Appendix

I. Table 1

Medication Class	Medication Names
Angiotensin-converting enzyme (ACE) inhibitors	Lisinopril, captopril, enalapril, benazepril, fosinopril, quinapril, ramipril, perindopril, trandolapril
Angiotensin II receptor blockers (ARB)	Losartan, olmesartan, valsartan, telmisartan, irbesartan, candesartan, azilsartan, eprosartan.
Beta-blockers	Propranolol, timolol, nadolol, metoprolol, carvedilol, bisoprolol, atenolol, nebivolol, acebutolol, pindolol, sotalol, bucindolol
Lipid lowering therapies	Atorvastatin, rosuvastatin, simvastatin, pravastatin, lovastatin, fluvastatin, pitavastatin, ezetimibe, bempedoic acid (Nexletol), bempedoic acid and ezetimibe (Nexlizet)
Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors	evolocumab (Repatha), praluent (Alirocumab)
Antiplatelet therapy	Aspirin, clopidogrel, ticagrelor, prasugrel, cangrelor

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
Medications for Weight Management	Chronic weight management

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated MASH criteria to include non-invasive testing and one comorbid condition. Updated relevant supporting evidence	09/2025
Updated MACE reduction criteria for the definition of established cardiovascular disease to include symptomatic carotid artery disease and symptomatic coronary artery disease. Live 8/18: Added policy criteria for semaglutide in treatment of nonalcoholic steatohepatitis (NASH)/ Metabolic Dysfunction-Associated Steatohepatitis (MASH) with supporting evidence.	05/2025
Policy created	05/2024

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP031

Description

Granulocyte-colony stimulating factors (G-CSF) and granulocyte macrophage-CSF (GM-CSF) act on the hematopoietic cells by binding to specific cell surface receptors thereby stimulating the production, maturation, and activation of neutrophils.

Length of Authorization

- Initial: Four months
- Renewal: Four months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
filgrastim (Neupogen)	300 mcg/mL vial	• Bone marrow transplant • Peripheral progenitor cell (PBPC) mobilization and transplant • Prophylactic use in patients with non-myeloid malignancy • Treatment of chemotherapy-induced febrile neutropenia • Neutropenic complications from prior chemotherapy cycle • Acute myeloid leukemia (AML) patient following induction or consolidation chemotherapy • Bone marrow transplantation failure or engraftment delay • Severe chronic neutropenia • Myelodysplastic syndrome • Exposure to myelosuppressive doses of radiation • Warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome†	15 prefilled syringes or vials per 30-day supply
	300 mcg/0.5mL syringe		
	480 mcg/1.6mL vial		
	480 mcg/0.8mL syringe		
filgrastim-sndz (Zarxio)*	300 mcg/0.5mL syringe		
	480 mcg/0.8mL syringe		
filgrastim-aafi (Nivestym)	300 mcg/mL vial		
	300 mcg/0.5mL syringe		
	480 mcg/1.6mL vial		
	480 mcg/0.8mL syringe		
tbo-filgrastim (Granix)	300 mcg/mL vial		
	300 mcg/0.5mL syringe		
	480 mcg/1.6mL vial		
	480 mcg/0.8mL syringe		
filgrastim-ayow (Releuko)	300 mcg/mL vial		
	300 mcg/0.5mL syringe		
	480 mcg/1.6mL vial		
	480 mcg/0.8mL syringe		
sargramostim (Leukine)	250 mcg/mL vial		
filgrastim-txid (Nypozi)	300mg/0.5mL PF syringe		
	480mg/0.8mL PF syringe		

* There is no prior authorization required for Zarxio (filgrastim-sndz) unless requesting above the quantity limit noted above

† Higher doses may be needed for the treatment of WHIM syndrome. Quantity limit exceptions will be reviewed on a case by case basis.

Initial Evaluation

- I. **Neupogen (filgrastim), Nivestym (filgrastim-aafi), Granix (tbo-filgrastim), and Releuko (filgrastim-ayow), Nypozi (filgrastim-txid)** may be considered medically necessary when the following criteria below are met:

Zarxio is the preferred short-acting G-CSF

- **Patients must have failed, or have a contraindication, or intolerance to Zarxio prior to consideration of any other short-acting G-CSF**
 - There is no prior authorization* required for Zarxio unless requesting above the quantity limit noted above.

A. A diagnosis of:

1. **Peripheral Blood Progenitor Cell (PBPC) mobilization and transplant; OR**
2. **Patient who experienced a neutropenic complication from a prior cycle of the same chemotherapy; OR**
3. **Bone Marrow Transplant (BMT); OR**
4. **Bone Marrow Transplantation (BMT) failure or Engraftment Delay; OR**
5. **Patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome); OR**
6. **Acute Myeloid Leukemia (AML) patient following induction or consolidation chemotherapy; OR**
7. **Prophylactic use in patients with non-myeloid malignancy; AND**
 - i. Member is undergoing myelosuppressive chemotherapy with an expected incidence of febrile neutropenia of 20% or greater; **OR**
 - ii. Member is undergoing myelosuppressive chemotherapy with an expected incidence of febrile neutropenia of 10% or greater **AND** has one or more of the following co-morbidities:
 - a. Age 65 years or older AND receiving full dose intensity chemotherapy
 - b. History of recurrent febrile neutropenia from chemotherapy
 - c. Extensive prior exposure to chemotherapy
 - d. Previous exposure of pelvis, or other areas of large amounts of bone marrow, to radiation
 - e. Pre-existing neutropenia ($ANC \leq 1000/mm^3$) or bone marrow involvement with tumor
 - f. Member has a condition that can potentially increase the risk of serious infection (i.e. HIV/AIDS)
 - g. Infection/open wounds
 - h. Recent surgery
 - i. Poor performance status
 - j. Poor renal function (creatinine clearance <50)
 - k. Liver dysfunction (elevated bilirubin >2.0)
 - l. Chronic immunosuppression in the post-transplant setting including organ transplant; **OR**
8. **Myelodysplastic Syndrome; AND**
 - i. Endogenous serum erythropoietin level of ≤ 500 mUnits/mL; **AND**

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- ii. Member has lower risk disease (i.e., defined as IPSS-R [Very Low, Low, Intermediate], IPSS [Low/Intermediate-1], WPSS [Very Low, Low, Intermediate]); **AND**
 - iii. Used for treatment of symptomatic anemia in patients without del(5q); **AND**
 - iv. Member is receiving concurrent therapy with Erythropoiesis Stimulating Agents (ESA); **AND**
 - a. Member has ring sideroblasts < 15% and will use in combination with lenalidomide following no response (despite adequate iron stores) or loss or response to an ESA alone; **OR**
 - b. Member has ring sideroblasts ≥ 15%; **OR**
- 9. Treatment of chemotherapy-induced febrile neutropenia; AND**
- i. Member has been on prophylactic therapy with filgrastim; **OR**
 - ii. Member has not received prophylactic therapy with a granulocyte colony stimulating factor; **AND**
 - a. Member has one or more of the following risk factors for developing infection-related complications:
 - i. Sepsis Syndrome
 - ii. Age >65
 - iii. Absolute neutrophil count [ANC] <100/mcL
 - iv. Duration of neutropenia expected to be greater than 10 days
 - v. Pneumonia or other clinically documented infections
 - vi. Invasive fungal infection
 - vii. Hospitalization at the time of fever
 - viii. Prior episode of febrile neutropenia; **OR**
- 10. Severe chronic neutropenia; AND**
- i. Member has an absolute neutrophil count (ANC) < 500/mm³; **AND**
 - ii. Member has a diagnosis of one of the following:
 - a. Congenital neutropenia
 - b. Cyclic neutropenia
 - c. Idiopathic neutropenia; **OR**
- 11. Management of CAR-T related Toxicity; AND**
- i. Member has been receiving therapy with CAR T-cell therapy (e.g. tisagenlecleucel (Kymriah), axicabtagene ciloleucel (Yescarta), etc.); **AND**
 - ii. Member is experiencing neutropenia related to their therapy; **OR**
- 12. Warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome; AND**
- i. Documented genotype-confirmed mutation of *CXCR4* consistent with WHIM phenotype; **AND**
 - ii. Documentation of severe symptoms and complications associated with WHIM syndrome (e.g., history of recurrent infections, chronic neutropenia, history of lymphopenia, history of hypogammaglobulinemia, detected myelokathexis, refractory or recalcitrant warts, etc.); **AND**

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- iii. Documentation of absolute neutrophil count (ANC) < 1500 cells/μL that is not related to medication, chemotherapy, or secondary to viral infection
- II. **Leukine (sargramostim)** may be considered medically necessary when the following criteria below are met:
 - A. **High-Risk Neuroblastoma; AND**
 - 1. Used in combination with GD2-binding monoclonal antibodies (i.e., naxitamab, dinutuximab, etc.) for the treatment of high-risk neuroblastoma; **OR**
 - B. Both of the following (1 and 2):
 - 1. A diagnosis of one of the following:
 - i. **Peripheral Blood Progenitor Cell (PBPC) mobilization and transplant; OR**
 - ii. **Patient who experienced a neutropenic complication from a prior cycle of the same chemotherapy; OR**
 - iii. **Bone Marrow Transplant (BMT); OR**
 - iv. **Bone Marrow Transplantation (BMT) failure or Engraftment Delay; OR**
 - v. **Patients acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome); OR**
 - vi. **Acute Myeloid Leukemia (AML) patient following induction or consolidation chemotherapy; OR**
 - vii. **Treatment of chemotherapy-induced febrile neutropenia; AND**
 - a. Member has been on prophylactic therapy with filgrastim; **OR**
 - b. Member has not received prophylactic therapy with a granulocyte colony stimulating factor; **AND**
 - i. Member has one or more of the following risk factors for developing infection-related complications:
 - 1. Sepsis Syndrome
 - 2. Age >65
 - 3. Absolute neutrophil count [ANC] <100/mcL
 - 4. Duration of neutropenia expected to be greater than 10 days
 - 5. Pneumonia or other clinically documented infections
 - 6. Invasive fungal infection
 - 7. Hospitalization at the time of fever
 - 8. Prior episode of febrile neutropenia; **AND**
 - 2. Treatment with Zarxio (filgrastim-sndz) has been ineffective, contraindicated, or not tolerated

Renewal Evaluation

- I. Same as initial prior authorization policy criteria.

Supporting Evidence

- I. Indications listed under section I are supported by FDA-labeled indication(s) or are recommended per Compendia.

- II. Quantity limits are based on usual FDA dosing of once daily until complete blood count (CBC) or absolute neutrophil count (ANC) has returned to an appropriate range. Generally, chemotherapy is administered every 2-3 weeks, whereby frequency of filgrastim is not expected to be needed for greater than two weeks. For other indications, such as transplant, WHIM syndrome, myelodysplastic syndrome, or chronic neutropenia, therapy is continued until adequate neutrophil recovery is achieved. Accordingly, quantity exceptions may be considered when frequent administration of filgrastim is deemed medically necessary.
- III. Duration of approval is based on usual duration of chemotherapy or radiation therapy cycle. There is no guideline consensus on optimal duration of G-CSF or GM-CSF treatment or prophylaxis, therefore continued use is driven by clinical scenario and lab monitoring.
- IV. Risk of developing febrile neutropenia is related to intensity and toxicity of chemotherapy regimen, as well as patient-specific factors. Expected incidence of febrile neutropenia percentages for myelosuppressive chemotherapy regimens can be found in the NCCN Hematopoietic Growth Factors Clinical Practice Guideline at [NCCN.org](https://www.nccn.org). NCCN and ASCO guidelines recommend use of a G-CSF for prophylaxis when risk is 20% or greater. When risk is between 10-20%, prophylactic G-CSF is recommended when patients have one or more of the risk factors listed above. Routine prophylaxis with G-CSF for febrile neutropenia when risk is less than 10% is not recommended.
- V. In myelodysplastic syndromes (MDS), G-CSF may be used in combination with an erythropoiesis-stimulating agent (ESA) when patients have symptomatic anemia, as G-CSF can boost erythroid response. Likelihood of erythroid response is influenced by serum erythropoietin, MDS prognostic category, presence of ring sideroblasts, and other factors, therefore criteria outlined above follow NCCN guidelines to target the patient population expected to achieve a response.
- VI. In the setting of high risk neuroblastoma (HRNB), GD2-binding monoclonal antibodies are labeled for use in combination with GM-CSF products specifically.
- VII. Warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome is a rare immunodeficiency and a congenital neutropenic disorder that results from impaired leukocyte trafficking. Warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome presents with chronic neutropenia, lymphopenia, monocytopenia, recurrent infections, and warts. Individuals with WHIM syndrome are susceptible to bacterial infections and human papillomavirus (HPV) infections and cancer risk. Warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome as an autosomal dominant condition is predominately caused by gain-of-function variants in CXCR4, which is a key regulator of the mobilization of white blood cells (neutrophils and lymphocytes) with a prevalence of less than 1 in 1,000,000. Treatment is intended to target symptoms of WHIM and includes the use of granulocyte-colony stimulating factor (G-CSF) to correct neutropenia, immunoglobulin (Ig) for hypogammaglobulinemia, and antibiotics for infections.
- VIII. As of August 2024, WHIM syndrome does not have a specific ICD-10 code; however, ICD-10 codes of D81.8 "Other combined immunodeficiencies" or D89.9 "Disorder involving the immune mechanism, unspecified" may apply to mavoxixafor (Xolremdi). The confirmation of documented genotype-confirmed mutation of CXCR4 consistent with WHIM phenotype should be done in those presenting with common symptoms of WHIM, such as history of recurrent infections, chronic neutropenia, lymphopenia, monocytopenia, hypogammaglobulinemia, recalcitrant or recurrent warts, and presence of neutropenia based on absolute neutrophil ANC count <1500 cells/ μ L.

- IX. Long-term efficacy and safety of G-CSF therapy has been demonstrated in treating neutropenia and preventing infection in various conditions, including in patients who have chronic neutropenia that are not caused by cancer treatment. Several case reports have been published on the off-label use of G-CSFs in WHIM syndrome, which resulted in a correction in neutropenia; however, limited evidence to suggest efficacy in treating lymphopenia. While their use is off-label, the correction for neutropenia with G-CSF therapy has been the standard in treating patients with severe neutropenia. In absence of clinical guidelines or guidance on therapy sequencing, the use of G-CSF therapy is considered an appropriate first step in the treatment of severe neutropenia as it provides an efficacious and cost-effective treatment option for patients with WHIM syndrome.
- X. While G-CSF have not been directly compared to mavorixafor (Xolremdi), they have been studied against a CXCR4 inhibitor in WHIM syndrome (NCT02231879) in patients with ANC <1500cells/ μ L and a history of severe infection. In a Phase 3 crossover trial of plerixafor versus G-CSF for the treatment of WHIM syndrome (N = 19), twice daily plerixafor was non-superior to twice daily G-CSF for total infection severity score ($P = 0.54$). The study was not designed to answer whether plerixafor is non-inferior to G-CSF for infection severity; however, no differences between the G-CSF and plerixafor arms were found for any infection outcome measures. In exploratory endpoints, plerixafor was non-inferior to G-CSF for maintaining neutrophil counts of >500 cells/ μ L ($P = 0.023$) and was superior to G-CSF for maintaining lymphocyte counts >1000cells/ μ L ($p < 0.0001$). Complete regression of a subset of large wart areas occurred on plerixafor in 5 of 7 patients with major wart burdens at baseline. There were no significant differences in drug preference or quality of life or the incidence of drug failure or serious adverse events. The exploratory endpoints suggested that plerixafor may be non-inferior to G-CSF for durably increasing the ANC and may have an advantage over G-CSF for elevating the ALC, for wart regression, and for limiting bone pain. Given the above, the risks of mavorixafor (Xolremdi) are generally comparable to those of approved G-CSF and CXCR4 antagonists.
- XI. Quantity limits for G-CSF in WHIM syndrome may be needed for up to two doses per day supply, based on prior studies in WHIM syndrome and chronic neutropenia; therefore, quantity limit exceptions may be granted in these cases as treatment efficacy is based on ANC.
- XII. All FDA-approved biosimilars undergo a rigorous testing process to compare safety, purity, and potency between the proposed biosimilar and the parent or originator product, otherwise known as the reference product, to ensure there are no clinically meaningful differences. Only minor differences between products are allowed, such as in clinically inactive components. Biosimilars may be approved for all, or a subset, of the indications for the reference product. It is not uncommon for biosimilars to have fewer labeled indications if the reference product has remaining patent or exclusivity rights. It can be expected that biosimilar products will have the same clinical efficacy and safety profile as the reference product due to thorough FDA testing. With a goal to increase access to high-quality, cost-effective care, biosimilars may fill an unmet need as a more affordable alternative to brand biologic therapies. Notably, NCCN Guidelines similarly recommend that FDA-approved biosimilars be used as substitutes for originator filgrastim and pegfilgrastim. In addition, ASCO recommends that pegfilgrastim, filgrastim and biosimilars be considered therapeutically equivalent, with product selection being based on convenience, cost and clinical situation (i.e., chemotherapy frequency). As such, trial of preferred short-acting G-CSF biosimilar Zarxio (filgrastim-sndz) is required prior to approval of non-preferred filgrastim products.

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Related Policies

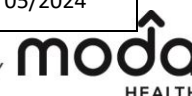
Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
Long-acting Granulocyte Colony Stimulating Factor (G-CSF)	Prophylactic use in patients with non-myeloid malignancy
	Neutropenic complications from prior chemotherapy cycle
	Exposure to myelosuppressive doses of radiation
	Bone marrow transplantation failure or engraftment delay
	Peripheral progenitor cell (PBPC) mobilization and transplant
Mavorixafor (Xolremdi)	WHIM syndrome

Policy Implementation/Update:

Action and Summary of Changes	Date
Added Nypozi (filgrastim-txid) to the policy	12/2024
Added pathway to coverage in the setting of WHIM syndrome. Updated supporting evidence, quantity limits table, references, and related policies sections.	08/2024
Updating policy formatting to align to medical policy and references. Added criteria to allow use of Leukine for the treatment of high-risk neuroblastoma prior to Zarxio when used in combination with anti-GD2 therapy.	05/2024

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Updated policy supporting evidence and references. Added related policies table.	08/2022
Added Releuko (filgrastim-ayow) to policy in the non-preferred position	04/2022
Updated quantity level limit to allow 15 doses per 30-day supply	12/2019
Policy title change, designate Zarxio as a preferred product, add “No PA Required” to Initial Evaluation Section 1 boxed information	10/2019
Previous Reviews	12/2018
Added Nivestym, biosimilar to Neupogen	10/2018
Previous Reviews	02/2018; 07/2018
Criteria update. Zarxio is the preferred short-acting G-CSF	2/2017

Policy Type: PA

Pharmacy Coverage Policy: UMP106

Description

Simvastatin (Zocor) is an orally administered 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor used to reduce LDL-C and prevent cardiovascular events.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
Simvastatin (Zocor)	80 mg tablets	Prevention of cardiovascular events/cardiovascular disease and reduce the risk of atherosclerotic cardiovascular disease, homozygous familial hypercholesterolemia	30 tablets/30 days

Initial Evaluation

- I. **Simvastatin 80 mg (Zocor)** may be considered medically necessary when the following criteria below are met:
 - A. Member has been established and stabilized on the 80 mg dose for a duration of 12 or more months without evidence of muscle toxicity (e.g. myopathy, rhabdomyolysis) within the past 12 months.

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent; **AND**
- II. Member has exhibited improvement or stability of disease symptoms; **AND**
- III. Member has not experienced symptoms of muscle toxicity (e.g. myopathy, rhabdomyolysis).

Supporting Evidence

- I. In 2011, the FDA issued a dose limitation on simvastatin 80 mg stating that it should not be started in new patients and should only be used in patients who have been taking this dose for 12 months or more without evidence of muscle injury (myopathy). Furthermore, 2018 AHA/ACC guidelines note simvastatin 80 mg/day is not recommended due to increased risk of myopathy. If patient is unable to achieve LDL-C goal with simvastatin 40 mg/day, switch to a high-intensity statin.

- II. The SEARCH trial was a seven-year, randomized, double-blind study that compared the efficacy and safety of simvastatin 80 mg versus simvastatin 20 mg, with or without vitamin B12 and folate in survivors of myocardial infarction.
- Incidence of major vascular events between the simvastatin 80 mg group and simvastatin 20 mg group was 24.5% vs 25.7%, respectively (95% CI 0.88, 1.01, p=0.10).
 - 0.9% of patients in the simvastatin 80 mg group experienced myopathy versus 0.02% in the simvastatin 20 mg group. Risk for myopathy and rhabdomyolysis was highest in the first 12 months of therapy.

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Updates to wording of initial criteria in efforts to clarify policy intent	05/2021
Criteria transitioned to policy with supporting evidence section added.	10/2019
New criteria	01/2017

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP259

Description

Sirolimus (Hyftor) is a topically administered mammalian target of rapamycin (mTOR) inhibitor.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
sirolimus (Hyftor)	Facial angiofibroma associated with Tuberous Sclerosis	0.2% topical gel	6-11 years of age: 20 grams/30 days
			12 years of age and older: 30 grams/30 days

Initial Evaluation

- I. **Sirolimus (Hyftor)** may be considered medically necessary when the following criteria are met:
 - A. Member is 6 years of age or older; **AND**
 - B. Medication is prescribed by, or in consultation with, a dermatologist or neurologist; **AND**
 - C. Provider attestation that the member has facial angiofibroma, associated with tuberous sclerosis confirmed by genetic testing and/or clinical symptoms; **AND**
 - D. Provider attestation that facial angiofibroma is associated with one or more of the following: bleeding, intense itching, pain, change in physical appearance, recent enlargement, or recent increase in number of lesions; **AND**
 - E. Treatment with topical compounded sirolimus (gel, cream, or ointment) has been ineffective, contraindicated, or not tolerated; **AND**
 - F. Previous treatment with surgery (shave excision, cryotherapy, electrodesiccation, radiofrequency ablation, dermabrasion) has been ineffective, contraindicated, or not tolerated; **OR**
 1. Previous treatment with laser therapy (ablative laser resurfacing, pulse dye laser) has been ineffective, contraindicated, or not tolerated.
- II. Sirolimus (Hyftor) is considered investigational when used for all other conditions, including but not limited to:
 - A. Tufted angiomas
 - B. Fibroma or angiofibroma not associated with tuberous sclerosis complex
 - C. Non FDA-approved dermatologic conditions

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Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Documentation that member has exhibited improvement or stability in extent and/or severity of angiofibroma (e.g., reduction in angiofibroma size and redness).

Supporting Evidence

- I. Tuberous sclerosis complex (TSC) is a rare genetic multisystem disorder associated with the formation of benign tumors in various organ systems throughout the body, most commonly including the skin, brain, eyes, heart, kidneys, and lungs. Skin manifestations of TSC occur in up to 95% of individuals and include facial angiofibromas, hypomelanotic macules, fibrous plaques, Shagreen patches, and ungual fibromas. Most patients with TSC present with angiofibromas with onset commonly occurring in early childhood or early adulthood. Angiofibromas are benign reddish pink bumps located on the face, and without treatment they can cause facial disfigurement, bleeding, itching, erythema, and significant psychosocial consequences.
- II. Per the International Tuberous Sclerosis Complex Diagnostic Criteria Surveillance and Management Recommendations, the diagnosis of tuberous sclerosis should be confirmed by genetic testing through identification of either a TSC1 or TSC2 pathogenic mutation in DNA from normal tissue. In the absence of TSC mutations, diagnosis can be made through identification of clinical features including but not limited to fibrous cephalic plaque, hypomelanotic macules, ungual fibromas, Shagreen patch, multiple retinal hamartomas, cortical dysplasia, subependymal nodules, subependymal giant cell astrocytoma's, cardiac rhabdomyoma, lymphangioleiomyomatosis, and angiomyolipomas.
- III. While there are limited treatment options for this condition, the International Tuberous Sclerosis Complex Diagnostic Criteria Surveillance and Management Recommendations recommend the use of topical compounded sirolimus (category 1 recommendation, based on a high-level of evidence and uniform consensus). Studies have evaluated compounded formulations ranging from 0.1% to 1% in a variety of vehicles. Smaller and flatter appearing lesions tend to respond better to topical sirolimus, so early treatment is recommended. Sirolimus (Hyftor) has not been evaluated against compounded sirolimus for the treatment of TSC angiofibroma, therefore comparative efficacy and safety remain uncertain. However, the chemical entity in both products is the same, therefore they are expected to provide similar safety and efficacy, even in the absence of a commercially available, FDA-labeled indication for compounded sirolimus. Further, given the long-established safety, efficacy, and cost effectiveness of compounded sirolimus, trial is required prior to use of sirolimus (Hyftor).
- IV. Guidelines recommend surgical approaches (category 2B, based on lower-level evidence and consensus that the intervention is appropriate) for angiofibromas rapidly changing in size and/or number, causing pain, bleeding, irritation, disfigurement, or impaired function. These procedures include shave excision, cryotherapy, electrodesiccation, radiofrequency ablation,

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dermabrasion, and laser therapy. They have been standardly used for angiofibroma management, though patients may not be candidates for surgery depending on anesthetic risk, age, active infection, uncontrolled diabetes, pregnancy, etc. Contraindications for laser therapy may include malignant carcinoma, irradiation of neck, epilepsy, exposure of retina, cognitive impairment, and pregnancy. Specifically, younger children may benefit from pulsed-dye laser therapy and adolescence ablative laser therapy to reduce facial erythema.

- V. The FDA-approval of sirolimus (Hyftor) was based off a phase 3, 12-week, multicenter, randomized, double-blind, placebo-controlled trial. The study population included 62 adults and pediatric patients greater than 6 years of age, with a definitive diagnosis of TSC, 3 or more reddish papules of facial angiofibromas (> 2 mm diameter), and a past difficulty with or did not want laser or surgical therapy. The concurrent use of any mTOR inhibitor, topical tacrolimus, topical steroids, topical antibiotics, topical vitamin D, adapalene, benzyl peroxide, ibuprofen piconol, resorcinol, and zinc-salicylic acid, were prohibited. Population characteristics were as follows: mean age 22 years (range of 6-53 years), 42% of patients had intellectual impairment, 60% had epilepsy, 28% had prior mTOR use (including topical sirolimus), and 32% had prior laser therapy, surgical resection, or liquid nitrogen therapy. The primary endpoint was composite improvement of angiofibroma size and color at week 12, which was met with 5 (17%) improved and 13 (43%) markedly improved in the sirolimus group compared to zero participants in the placebo group, with 84% rated unchanged. The secondary endpoints were response rates for composite, size, color, and plaques, and change in Dermatology Life Quality Index (DLQI) and Children's DLQI (CDLQI). The response rates for size, color, and plaques were statistically significant while the change from baseline in DLQI and CDLQI was not. The most common adverse events included dry skin (40%), application site irritation (37%), and itching (17%). Overall, this was a well-designed phase 3 clinical trial that showed statistical improvement in composite response rate and individual size, color and plaque response rates, however clinical meaningfulness of these endpoints and measurement tool remain unknown. Applicability to the larger TSC population is limited due to a large proportion of the population having previously been treated with surgery, laser or mTOR inhibitor therapy.
- VI. The initial authorization length of three months is supported by clinical study duration of 12 weeks and prescribing information guidance which indicates that if symptoms do not improve by week 12 of treatment, prescriber should reevaluate the need for continuation of the medication.
- VII. Quantity limits are based on the maximum daily doses used in pivotal study and as indicated by the FDA, and are expected to be sufficient, even if a large majority of the face is impacted. If symptoms do not improve within 12 weeks of consistent use and excessive quantities are needed, alternative treatment strategies that have the potential to be more efficacious and cost effective should be considered.

References

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5. UpToDate. Tuberous sclerosis complex: Genetics, clinical features, and diagnosis. Updated April 6, 2022. Accessed May 5, 2022.
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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
everolimus (Afinitor®, Afinitor Disperz®)	Partial seizure, adjunct, tuberous sclerosis syndrome
	Angiomyolipoma of the kidney, tuberous sclerosis syndrome
	Breast cancer, advanced, HR+, HER2 -, in combination with exemestane after failure with letrozole or anastrozole
	Subependymal giant cell astrocytoma
	Renal cell carcinoma, advanced disease
	Neuroendocrine tumor, gastrointestinal, lung or pancreatic, unresectable locally advanced or metastatic
cannabidiol (Epidiolex®)	Tuberous Sclerosis Complex
	Lennox-Gastaut Syndrome
	Dravet Syndrome

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	07/2022

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP153

Split Fill Management*

Description

Sonidegib (Odomzo) is an orally administered Hedgehog pathway inhibitor.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
sonidegib (Odomzo)	200 mg capsule	Basal cell carcinoma of the skin, locally advanced	30 capsules/30 days

Initial Evaluation

- I. Sonidegib (Odomzo) may be considered medically necessary when the following criteria below are met:
 - A. Member is 18 years of age or older; **AND**
 - B. Medication is prescribed by, or in consultation with, an oncologist or dermatologist; **AND**
 - C. Sonidegib (Odomzo) will not be used in combination with any other oncologic medication; **AND**
 - D. A diagnosis of **locally advanced basal cell carcinoma (BCC)** when the following are met:
 1. Basal cell carcinoma has recurred or progressed after radiation or surgery, unless both are contraindicated; **AND**
 2. The member has not progressed on any other oncologic medication (e.g., has not progressed on vismodegib [Erivedge]); **AND**
 3. Provider attestation that the member, either male or female, has been counseled on the teratogenicity and embryo-fetal toxicity risks with sonidegib (Odomzo).
- II. Sonidegib (Odomzo) is considered investigational when used for all other conditions, including but not limited to:
 - A. Metastatic basal cell carcinoma
 - B. Acute leukemia
 - C. Breast cancer
 - D. Medulloblastoma
 - E. Multiple myeloma
 - F. Myelofibrosis

- G. Prostate cancer
- H. Breast cancer
- I. Ovarian cancer
- J. Graft versus host disease
- K. Pancreatic cancer
- L. Lung cancer
- M. Hepatocellular carcinoma

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Sonidegib (Odomzo) is prescribed by, or in consultation with, an oncologist or dermatologist; **AND**
- IV. A diagnosis of **locally advanced basal cell carcinoma**; **AND**
 - A. Clinical response to therapy, such as improvement or stabilization of disease, or decrease or stabilization of tumor size or spread; **AND**
 - B. Provider attestation that the member, either male or female, has been counseled on the teratogenicity and embryo-fetal toxicity risks with sonidegib (Odomzo).

Supporting Evidence

- I. The safety and efficacy of sonidegib (Odomzo) was evaluated in a single, double-blind, single-drug trial. Those included had a diagnosis of locally advanced basal cell carcinoma (laBCC), and 144 adult subjects were randomized (2:1) to receive sonidegib (Odomzo) 800 mg or 200 mg daily. To be included in the trial, subjects were required to have lesions for which radiotherapy was contraindicated or inappropriate (e.g., limitations due to tumor location), that had recurred after radiotherapy, had unresectable disease in which surgical resection would result in substantial deformity, or that had recurred after prior surgical resection. The primary outcome was objective response rate (ORR) which was determined by a blinded central review committee according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST). A secondary measure was duration of response (DoR). The ORR was 56% (CI 43-68), and consisted of three (5%) complete responders, and 34 (52%) partial responders. The median duration of response was 26.1%; however, due to the single-drug nature of the trial, these results should be interpreted with caution.
- II. There were 128 subjects randomized to sonidegib (Odomzo) 800 mg daily. There was a lack of further benefit over the 200 mg dose relative to the safety profile.
- III. Sonidegib (Odomzo) carries a black box warning for embryo-fetal death or severe birth defects when administered to a pregnant woman. It is noted in the medication label that pregnancy be ruled out prior to initiating therapy. Those of reproductive potential should use contraception during treatment and for at least 20 months following the last dose. Males carry of risk of

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exposure through semen; thus, the package label recommends use of condoms with female partners during medication exposure and for at least eight months after the last dose.

- IV. Vismodegib (Erivedge) is FDA-approved for adults with metastatic and locally advanced basal cell carcinoma. Erivedge has an overlapping indication with sonidegib (Odomzo), and if disease progression has occurred on or after one of these therapies, there is currently insufficient evidence regarding safety and/or efficacy of the other. One published piece of literature evaluated sonidegib (Odomzo) in those that were resistant to vismodegib (Erivedge); however, this trial included only nine subjects all of which showed no response to sonidegib (Odomzo) or were not evaluable for safety and/or efficacy. Available evidence disfavors use of sequential Hedgehog pathway inhibitors.

Investigational or Not Medically Necessary Uses

- I. There is currently insufficient evidence to support safety and/or efficacy of sonidegib (Odomzo) in the following settings:
- A. Metastatic basal cell carcinoma
 - B. Acute leukemia
 - C. Breast cancer
 - D. Medulloblastoma
 - E. Multiple myeloma
 - F. Myelofibrosis
 - G. Prostate cancer
 - H. Breast cancer
 - I. Ovarian cancer
 - J. Graft versus host disease
 - K. Pancreatic cancer
 - L. Lung cancer
 - M. Hepatocellular carcinoma

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

1. Odomzo [Package Insert]. Cranbury, NJ. Sun Pharmaceutical Industries, Inc. 2017.
2. Burness CB, Scott LJ. Sonidegib: A Review in Locally Advanced Basal Cell Carcinoma. Target Oncol. 2016;11(2):239-46.
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Policy Implementation/Update:

Date Created	October 2015
Date Effective	November 2015
Last Updated	November 2019
Last Reviewed	November 2019

Action and Summary of Changes	Date
Prior authorization transitioned to policy. Addition of age edit, clarification and addition of requirements regarding previous therapies and use of sonidegib (Odomzo) monotherapy. Renewal duration increased for six to 12 months.	11/2019

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP244

Split Fill Management*

Description

Sotorasib (Lumakras) is an orally administered selective inhibitor of Kirsten Rat Sarcoma viral oncogene homologue (KRAS) and targets tumors harboring KRAS G12C mutation.

Length of Authorization

- Initial: 6 months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
sotorasib (Lumakras)	120 mg tablets	Non-Small Cell Lung Cancer (NSCLC), locally advanced or metastatic with a KRAS G12C mutation	240 tablets/30 days
	240 mg tablets		60 tablets/30 days
	320 mg tablets	Colorectal cancer, metastatic with a KRAS G12C mutation	60 tablets/30 days

Initial Evaluation

- I. **Sotorasib (Lumakras)** may be considered medically necessary when the following criteria below are met:
 - A. The member is 18 years of age or older; **AND**
 - B. The medication is prescribed by, or in consultation with, an oncologist; **AND**
 - C. Medication is not used in combination with any other oncology therapy unless specified below; **AND**
 - D. A diagnosis of **metastatic (stage IV) colorectal cancer (mCRC)**; **AND**
 1. The member has confirmed KRAS G12C mutation; **AND**
 2. The member has been previously treated with a fluoropyrimidine (e.g., fluorouracil, capecitabine, etc.), oxaliplatin, or irinotecan-based chemotherapy; **AND**
 3. The member has not had disease progression on prior KRAS G12C inhibitor therapy (i.e., adagrasib [Krazati]); **AND**
 4. Treatment will be used in combination with panitumumab (Vectibix)
- II. **Sotorasib (Lumakras)** is considered investigational when used for all conditions, including but not limited to:
 - A. Other solid tumors harboring KRAS G12C mutation
 - B. Non-Small Cell Lung cancer (NSCLC)

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Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Clinical documentation of response to treatment (e.g., stabilization of disease, decrease in tumor size or tumor spread, lack of disease progression); **AND**
- IV. The medication will be used in combination with panitumumab (Vectibix) in the setting of metastatic (stage IV) colorectal cancer (mCRC).

Supporting Evidence

- I. Sotorasib (Lumakras) is the first therapy to receive an accelerated FDA-approval for advanced or metastatic NSCLC that harbors a KRAS G12C mutation. It is also the first orally administered drug in this setting. Sotorasib (Lumakras) was FDA approved in January 2025 in combination with panitumumab (Vectibix) for treatment of adults with metastatic colorectal cancer (mCRC) with KRAS G12C-mutation as determined by an FDA approved-test, who received prior fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy.
- II. Colorectal cancer (CRC) is the third most prevalent cancer worldwide and the second most common cause of cancer death in the United States. Initial clinical presentation as mCRC occurs in approximately 20% of patients and nearly 70% of patients with localized disease eventually develop metastases. In 2023, approximately 150,000 individuals will be diagnosed with CRC and over 50,000 individuals will die from the disease. Given the complexity of management of mCRC, the treatment of mCRC must be initiated by, in or consultation with, an oncologist.
- III. KRAS mutation presents in more than 50% of CRC cases. The KRAS glycine-to-cysteine mutation at codon 12 (KRAS G12C) occurs in up to 4% of patients and is associated with short responses to standard chemotherapy and worse overall survival (OS) compared to wildtype tumors.
- IV. The National Comprehensive Cancer Network (NCCN) recommends fluoropyrimidine-based regimen in combination with oxaliplatin and/or irinotecan in the first- and second-line setting. In patients with mCRC with confirmed KRAS G12C mutation, sotorasib (Lumakras) and adagrasib (Krazati) with cetuximab (Erbix) or panitumumab (Vectibix) are recommended as second-line and subsequent therapy options (category 2A recommendation).
- V. Sotorasib (Lumakras) was studied in a Phase 3, open-label, randomized trial. Participants 18 years of older with confirmed KRAS G12C mutation that progressed on at least one previous line of therapy (fluoropyrimidine, oxaliplatin, and irinotecan with or without bevacizumab) and had not received previous treatment with KRAS G12C inhibitor were randomized 1:1:1 to receive sotorasib 960mg orally once daily with panitumumab IV 6mg/kg every 2 weeks (n=53), sotorasib 240mg once daily with panitumumab IV 6mg/kg every 2 weeks (n=53), or investigator choice (standard of care [SoC]) of trifluridine/tipiracil (Lonsurf) 35mg/m² (up to 80mg per dose) orally BID on days 1-5 and 8-12 every 28 days or regorafenib (Stivarga) 160mg orally once daily for 21 days out of the 28 day cycle (n=54). Baseline characteristics were generally balanced across groups, overall median age was 62 years, 49.4% were men, 15% of participants had one previous line of therapy, 85% had two or more previous lines of therapy. After a median follow-

up of 7.8 months, the primary endpoint of progression free survival (PFS) was 5.6 months for the high dose sotorasib (Lumakras) group, HR compared to SoC arm 0.48 (95% CI, 0.30 to 0.78; P=0.005) and 3.9 months in the low dose sotorasib (Lumakras) arm, HR 0.59 (95% CI, 0.37 to 0.95; P=0.036). Overall survival was not mature at PFS cutoff. Follow-up OS after 13.6 months reported 24, 28, and 30 deaths that occurred in the sotorasib (Lumakras) high and low dose and investigator choice. The high dose sotorasib (Lumakras) vs investigator choice HR was 0.7 (95%, 0.41-1.18, P=0.20) and low dose sotorasib (Lumakras) vs investigator choice HR was 0.83 (95%, 0.49-1.39, P=0.50), which trends in favor of sotorasib (Lumakras).

- VI. Treatment emergent adverse events of grade 3 or higher occurred in 35.8% in high dose sotorasib (Lumakras), 30.2% low dose sotorasib (Lumakras), and 43.1% in investigator choice. The most common adverse events in both sotorasib (Lumakras) groups were hypomagnesemia (28.3% and 30.2%) and dermatitis acneiform (22.6% and 37.7%), respectively. Sotorasib (Lumakras) and panitumumab (Vectibix) demonstrated a statistically significant difference in PFS compared to trifluridine/tipiracil (Lonsurf) and regorafenib (Stivarga) in the investigator choice group in treatment of advanced or metastatic colorectal cancer with KRAS G12C mutation. Progression free survival is a surrogate endpoint that has been strongly correlated with OS in first- and second-line treatment of mCRC. Although overall survival was not yet matured at PFS read out at 7.8 months it demonstrated a positive trend, favoring sotorasib (Lumakras) and panitumumab (Vectibix). It is not known how sotorasib + panitumumab compares to other KRAS G12C inhibitors.

Investigational or Not Medically Necessary Uses

- I. Sotorasib (Lumakras) is considered investigational when used for all conditions, including but not limited to
 - A. Other solid tumors harboring KRAS G12C mutation
 - B. Non-Small Cell Lung cancer (NSCLC)
 - i. Sotorasib (Lumakras) received accelerated FDA-approval as a subsequent-line therapy in the advanced or metastatic NSCLC, after progression on or after at least one prior systemic chemotherapy in May 2021.
 - ii. The National Comprehensive Cancer Network (NCCN) treatment guideline for NSCLC has given sotorasib (Lumakras) a Category 2A recommendation as a subsequent-line treatment for NSCLC harboring KRAS G12C mutation, after progression on or after conventional chemotherapy and/or immunotherapy.
 - iii. Most patients with NSCLC including KRAS-mutated tumors are treated with systemic chemotherapy, which includes carboplatin, pemetrexed, cisplatin, paclitaxel. Additionally, targeted immunotherapy such as inhibitors of programmed death-1 (PD-1) or programmed death-ligand 1 (PD-L1) (e.g., pembrolizumab (Keytruda), atezolizumab (Tecentriq), nivolumab (Opdivo)) are also recommended. Vascular Endothelial Growth Factor (VEGF) inhibitor ramucirumab (Cyramza) in combination with docetaxel (Taxotere) has shown success as a subsequent-line therapy in refractory disease.
 - iv. Sotorasib (Lumakras) was evaluated in CodeBreak100, an ongoing Phase 1 / 2, open-label, single-arm trial. Patients (N=126) with KRAS G12C mutated NSCLC, who had disease progression after chemotherapy and/ or immunotherapy were included. All patients received sotorasib (Lumakras) 960 mg orally once a day for a

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median 15.3 months. The primary efficacy was overall response rate (ORR). Key secondary outcomes were progression-free survival (PFS), duration of response (DoR), and overall survival (OS). Sotorasib (Lumakras) demonstrated an ORR of 37.1% (95% CI; 28.6, 46.2), which included 3.2% complete responses (CR) and 33.9% partial responses (PR). Additionally, participants in this cohort showed DoR of 11.1 months (95% CI; 6.9, NE), PFS 6.8 months (95% CI; 5.1, 8.2), and OS 12.5 months (95% CI; 10.0, NE).

- v. The safety of sotorasib (Lumakras) was based on trial participants (n=126) exposed to therapy. The most common adverse events include diarrhea, nausea, fatigue, and aspartate aminotransferase increase. Serious adverse events (grade 3 or higher) occurred in 42.1% patients and included dyspnea, pneumonitis, and elevation of liver enzymes.
- vi. In October 2023, the CodeBreak 200 study results were published. CodeBreak 200 is a Phase 3, randomized, open-label trial that evaluated efficacy of sotorasib (Lumakras) vs docetaxel in adult participants with metastatic NSCLC with KRAS G12C mutations. The primary endpoint, PFS, was 5.6 months [95% CI 4.3–7.8] vs 4.5 months [3.0–5.7] in the docetaxel arm; hazard ratio 0.66 [0.51–0.86]; p=0.0017. Overall survival (OS) was not statistically significant (HR 1.01 [95% CI, 0.77-1.33, p=0.53).
- vii. PFS is not a direct measure of benefit and cannot be used as a comprehensive measure of drug activity. Conventional chemotherapy agents (e.g., docetaxel, pemetrexed) and immune checkpoint inhibitors (e.g., nivolumab, pembrolizumab) remain practical and established therapeutic options for members, after progression on or after first-line therapies (e.g., platinum-based chemotherapy). Additionally, combination regimens containing angiogenesis inhibitors with conventional chemotherapy agents (e.g., ramucirumab and docetaxel) have been successful treatment options based on a Phase 3 clinical trial reporting OS of 10.5 months versus docetaxel monotherapy 9.1 months (HR 0.86; 95% CI 0.75, 0.98; p 0.023). Despite the accelerated FDA-approval, and category 2A recommendation from NCCN, continued approval of sotorasib (Lumakras) as a second-line treatment of NSCLC, remains contingent upon verification of clinical benefit in confirmatory trials.
- viii. As of April 2025, the FDA issued a complete response letter to the supplemental new drug application seeking full approval of Lumakras for KRAS G13C mutated NSCLC. The FDA's oncology Drugs advisory committee found that PFS data from confirmatory Phase 3 CodeBreak 200 trial could not be reliably interpreted as the difference in PFS in the sotorasib and docetaxel arms was small and there was no difference in OS.
- ix. Due to lack of conclusive clinical data to direct a path to curative therapies, NCCN guidelines for NSCLC notes that the best management for any patient with cancer is in a clinical trial setting, and participation in trial is especially encouraged. Patients participating in clinical trials receive regular care, often at leading health care facilities with experts in the field while participating in important medical research and further advancements in treatment, with close safety monitoring and follow-up. Participation in a clinical trial remains the most favorable treatment option for patients with advanced NSCLC. Additionally, expanded access program via manufacturer, as part of the ongoing clinical studies of

sotorasib (Lumakras), remains a practical option and an alternative path to treatment for qualifying patients.

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

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Related policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
regorafenib (Stivarga®) Policy	Gastrointestinal stromal tumor, metastatic colorectal cancer, hepatocellular carcinoma
trifluridine/tipiracil (Lonsurf®) Policy	Stomach or esophagogastric adenocarcinoma, metastatic colorectal cancer
encorafenib (Braftovi®), binimetinib (Mektovi®) Policy	Malignant melanoma (BRAF V600E mutation), metastatic colorectal cancer with BRAF V600E mutation
fruquintinib (Fruzaqla™)	Metastatic colorectal cancer (mCRC)
adagrasib (Krazati®)	Non-Small Cell Lung Cancer (NSCLC), advanced or metastatic with a KRAS G12C mutation, Colorectal cancer, metastatic with a KRAS G12C mutation

Policy Implementation/Update:

Action and Summary of Changes	Date
Added new FDA approved indication and coverage criteria for treatment of metastatic colorectal cancer with KRAS G12C mutation after progression on fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy. Moved NSCLC to separate E/I section and updated supporting evidence with the most up to date Phase 3 trial (CodeBreak-100) and the FDA's updated CRL (1/2/2025) requiring a new post market	06/2025

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study. Added solid tumors harboring KRAS G12C mutation to E/I section. Added related policies table. Added QL table to include 240mg tablet.	
Policy created	11/2021

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP278

Description

Sparsentan (Filspari) is an orally administered dual endothelin (ET_AR) and angiotensin II (AT₁R) receptor antagonist (DEARA) and inhibits endothelin-1 and angiotensin II, which may contribute to pathogenesis of immunoglobulin A nephropathy (IgAN). Atrasentan (Vanrafia) is an orally administered endothelin (ET_AR) antagonist to reduce proteinuria in adults with IgAN at risk of rapid disease progression.

Length of Authorization

- Initial: six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit*
sparsentan (Filspari)	Primary IgA nephropathy; at high risk of progression	200 mg tablet	30 tablets/30 days
		400 mg tablet	30 tablets/30 days
atrasentan (Vanrafia)		0.75 mg tab	30 tablets/30 days

*Quantity limit exceptions are not allowed.

Initial Evaluation

- I. **Sparsentan (Filspari) and atrasentan (Vanrafia)** may be considered medically necessary when the following criteria are met:
 - A. Member is 18 years of age or older; **AND**
 - B. Medication is prescribed by, or in consultation with, a nephrologist or immunologist; **AND**
 - C. Medication requested will not be used in combination atrasentan (Vanrafia), budesonide (Tarpeyo), sparsentan (Filspari), or iptacopan (Fabhalta); **AND**
 - D. A diagnosis of **Primary immunoglobulin A nephropathy (IgAN)** when the following are met:
 1. Diagnosis of Primary immunoglobulin A nephropathy (IgAN) has been confirmed by a kidney biopsy; **AND**
 2. Documentation of elevated protein levels in urine as indicated by proteinuria ≥ 1 g/day or urine protein to creatinine ratio (UPCR) ≥ 1.5 g/g; **AND**
 3. Member has an eGFR ≥ 30 mL/min/1.73m²; **AND**
 4. Member is not currently receiving dialysis; **AND**
 5. Member has not undergone a kidney transplant; **AND**
 - E. Treatment with a renin-angiotensin system (RAS) inhibitor [e.g., angiotensin converting enzyme (ACE) inhibitor (e.g., enalapril, lisinopril); angiotensin receptor blocker (ARB) (e.g., valsartan, irbesartan)] for ≥ 3 months has been ineffective, not tolerated, or all are contraindicated; **AND**
 - F. If the request is for **sparsentan (Filspari)**: Medication will not be used in combination with an angiotensin converting enzyme (ACE) inhibitor (e.g., enalapril, lisinopril), angiotensin

- receptor blocker (ARB) (e.g., valsartan, irbesartan), or a corticosteroid (e.g., prednisone, methylprednisolone, budesonide); **OR**
- G. If the request is for **atrasentan (Vanrafia)**: Medication will be used in combination with a renin-angiotensin system (RAS) inhibitor [e.g., angiotensin converting enzyme (ACE) inhibitor (e.g., enalapril, lisinopril); angiotensin receptor blocker (ARB) (e.g., valsartan, irbesartan)], unless not tolerated or contraindicated
- II. Sparsentan (Filspari) is considered investigational when used for all other conditions, including but not limited to:
- Secondary IgA nephropathy
 - Newly diagnosed IgAN without high risk of disease progression
 - IgAN-treatments in combination (e.g., atrasentan (Vanrafia), sparsentan (Filspari), budesonide (Tarpeyo), iptacopan (Fabhalta))
 - Focal segmental glomerulosclerosis (FSGS)
 - Chronic kidney disease (CKD) other than primary IgAN

Renewal Evaluation

- Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- Medication will not be used in combination with atrasentan (Vanrafia), budesonide (Tarpeyo), sparsentan (Filspari), iptacopan (Fabhalta): **AND**
- Member has an eGFR > 30 mL/min/1.73m²; **AND**
- Member is not currently receiving dialysis; **AND**
- Member has not undergone kidney transplant; **AND**
- Member has exhibited improvement or stability of disease symptoms (e.g., reduction in proteinuria <1 g/day or urine protein to creatinine ratio (UPCR) < 1.5 g/g); **AND**
- If the request is for **sparsentan (Filspari)**: Medication will be used as a monotherapy (i.e., not in combination with angiotensin converting enzyme (ACE) inhibitor (e.g., enalapril, lisinopril), angiotensin receptor blocker (ARB) (e.g., valsartan, irbesartan), or corticosteroid (e.g., prednisone, methylprednisolone, budesonide (Tarpeyo))); **OR**
- If the request is for **atrasentan (Vanrafia)**: Medication will be used in combination with a renin-angiotensin system (RAS) inhibitor [e.g., angiotensin converting enzyme (ACE) inhibitor (e.g., enalapril, lisinopril); angiotensin receptor blocker (ARB) (e.g., valsartan, irbesartan)], unless not tolerated or contraindicated

Supporting Evidence

- Sparsentan (Filspari) is a novel Dual Endothelin Angiotensin Receptor Antagonist (DEARA) that received accelerated FDA-approval in February 2023 for the reduction of proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression. Full approval was granted in September 2024 after positive confirmatory eGFR data. Atrasentan (Vanrafia) is a selective endothelin type A receptor (ET_AR) antagonist that received FDA accelerated approval in April 2025 to reduce proteinuria in adults with primary immunoglobulin

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A nephropathy (IgAN) at risk of rapid disease progression. Full approval of atrasentan (Vanrafia) is expected in 2026. Sparsentan (Filspari) and atrasentan (Vanrafia) have not been studied in pediatric population.

- II. Primary immunoglobulin A nephropathy, also called Berger's disease, is a rare kidney disorder characterized by deposits of immune complexes containing galactose-deficient IgA in the glomerular mesangium leading to glomerulosclerosis, and renal failure. Although previously considered a benign condition, IgAN is now recognized to cause end-stage renal disease (ESRD) in 30% of affected individuals.
- III. The Kidney Disease Improving Global Outcomes (KDIGO) guideline indicates IgAN can only be diagnosed with a kidney biopsy. While there are several prognostic scoring tools that have been developed to assist in predicting kidney outcomes of IgAN patients (i.e., MEST-C, International IgAN Prediction Tool, etc.) there are currently no validated diagnostic serum or urine biomarkers.
- IV. Due to the complexities related to diagnosis monitoring and management of IgAN patients, therapy for this disease space should be initiated by or in consultation with a specialist such as nephrologist or immunologist.
- V. There are no curative therapies for IgAN. Supportive care with blood pressure management, use of renin-angiotensin system (RAS) blockers (ACEis or ARBs), and lifestyle modifications are the recommended initial interventions for IgAN treatment. Patients with proteinuria level of ≥ 1 g/day (or urine protein to creatinine ratio (UPCR) > 1.5 g/g) despite 3 to 6 months of initial treatment, are at high risk of progression to kidney failure. KDIGO guideline for the management of glomerular diseases strongly recommends proteinuria reduction < 1 g/day as a treatment goal for high-risk IgAN.
- VI. Sparsentan (Filspari) is the first DEARA and the second drug approved for the treatment of IgAN. It follows IgAN-indicated budesonide (Tarpeyo). A nine-month course of glucocorticoids (e.g., prednisone, methylprednisolone) and/or other immunosuppressants (e.g., hydroxychloroquine, mycophenolate) have been used for the treatment of high-risk IgAN. However, their use may be limited by other prognostic factors (e.g., $\text{eGFR} > 30 \text{ mL/min/1.73 m}^2$), lack of strong clinical evidence, and considerations of treatment-related toxicities. Additionally, the KDIGO guideline recommends enrollment in a clinical trial for this patient population. Sparsentan (Filspari) may be considered a steroid-sparing alternative for the treatment of high-risk IgAN.
- VII. The accelerated FDA approval for sparsentan (Filspari) was based on interim analysis of a randomized, double-blind, active-controlled Phase 3 trial where patients were randomized 1:1 to either sparsentan (Filspari) 400 mg or irbesartan 300 mg once daily (PROTECT, N = 404). Adults with biopsy proven primary IgAN, proteinuria ≥ 1 g/day, $\text{eGFR} \geq 30 \text{ mL/min/1.73 m}^2$, and supportive therapy with an ACEi and/or ARB for ≥ 12 weeks were included in the study. Patients with secondary IgAN, documented history of immunosuppressant (including corticosteroids) use for ≥ 2 weeks within 3 months before screening, active CVD, hepatic or immune conditions were excluded. Baseline median proteinuria and mean eGFR in the sparsentan (Filspari) treatment arm were 1.8 g/day, and $56.9 \text{ mL/min/1.73 m}^2$, respectively. Half (51.5%) of patients in the treatment arm had urinary protein excretion > 1.75 g/day at baseline. The primary endpoint was met for the reported change in UPCR at week 36 versus baseline, which was -49.8% and -15% for sparsentan (Filspari) versus irbesartan (OR 0.6; 95% CI .5, 0.7; $p < 0.0001$). Additionally, 55% patients in the treatment arm achieved proteinuria < 1 g/day at week 36. A supportive secondary endpoint: change in UPCR at week 94 was also reported to be statistically significant (52% versus 11%; $p = 0.0002$).

- VIII. Conversion to full approval of sparsentan (Filspari) was based on the 2-year eGFR results from the PROTECT Study, where sparsentan (Filspari) delivered superior long-term kidney function preservation compared to irbesartan. The two-year efficacy data contained in the FDA-approved label was a modified intention to treat (ITT) analysis, as preferred by the FDA, evaluated data from all patients regardless of treatment discontinuation. In the final analysis of the 404 randomized patients, sparsentan (Filspari) significantly reduced the rate of decline in kidney function from baseline to Week 110 compared to irbesartan. In the ITT analysis included in the label, the mean eGFR slope from baseline to Week 110 was -3.0 mL/min/1.73 m²/year for sparsentan (Filspari) and -4.2 mL/min/1.73 m²/year for irbesartan, corresponding to a statistically significant treatment effect of 1.2 mL/min/1.73 m²/year (p=0.0168). The positive treatment effects on proteinuria compared to irbesartan that were observed at Week 36 were durable out to the two-year measurement period. Additional results from the PROTECT Study demonstrated the benefit of sparsentan (Filspari) on absolute eGFR accrued over time and by Week 110 resulted in a 3.8 mL/min/1.73 m² difference in the mean change from baseline between sparsentan (Filspari) and irbesartan.
- IX. During PROTECT clinical trial for sparsentan (Filspari), patients with a history of immunosuppressants, including corticosteroids, for more than 2 weeks within 3 months of screening were excluded. Efficacy and safety of sparsentan (Filspari) in combination with IgAN-indicated budesonide (Tarpeyo) and other systemic corticosteroids has not been evaluated. Due to the very high risk of adverse events, concurrent use of ACE inhibitors and ARB agents with sparsentan (Filspari) is contraindicated.
- X. During PROTECT clinical trial, a higher percentage of sparsentan (Filspari) treated patients reported treatment-emergent adverse event (TEAE) than irbesartan group (82.2% versus 73.3%), with dizziness (13%), peripheral edema (13%), hyperkalemia (10%), hypotension (10%), fatigue (8%), upper respiratory tract infections (6%), and acute kidney injury (4%) reported as the most common TEAE in the treatment arm. Kidney and urinary disorders were the most common severe adverse event (AE) reported in both arms leading to discontinuations (7.9% and 4.5% in the sparsentan (Filspari) and irbesartan arms, respectively). Results from the two-year trial showed that sparsentan (Filspari) was well tolerated with a clearly defined safety profile that has been consistent across all clinical trials conducted to date. Following engagement with the FDA, the Trave Therapeutics expects to submit an sNDA for a potential modification to the liver-monitoring REMS.
- XI. The real-world utility of sparsentan (Filspari) is limited by exclusion of patients with cardiovascular disorders, anemia (Hb< 9 g/dL), and pre-existing CKD, which are considered major prognostic concerns related to renal impairment and are critical risk factors associated with mortality in CKD. An open-label extension (OLE) for the PROTECT clinical trial is currently ongoing along with two additional clinical trials to evaluate sparsentan (Filspari) for the treatment of focal segmental glomerulosclerosis (FSGS).
- XII. The accelerated approval of atrasentan (Vanrafia) was based on the prespecified interim analysis of the ALIGN trial, a Phase 3, randomized, double-blind, placebo-controlled study involving 270 patients with biopsy-confirmed IgAN, persistent proteinuria ≥1.0 g/day, on a stable dose of maximally tolerated RASi. The study included two cohorts: a main cohort (340 patients) and an exploratory cohort (64 patients who were also on a stable dose of SGLT2i at baseline), which was independent of the main stratum and analyzed separately. Baseline mean eGFR in the atrasentan (Vanrafia) treatment arm was 1.5g/g and 59 mL/min/1.73m². The

geometric mean baseline UPCR was 1.5g/g samples from a 24-hour urine and 15% of patients had proteinuria >3.5 g/day. The trial excluded participants on chronic dialysis or kidney transplantation for end-stage kidney disease as these are considered clinical outcomes of interest. The efficacy analysis used to support the accelerated approval included the first 270 patients in the main cohort who reached the primary endpoint at week 36: was the percent change in urine protein-to-creatinine ratio (UPCR) from baseline. In the interim analysis, the geometric mean percentage change in the UPCR relative to baseline was significantly greater with atrasentan (Vanrafia) (-38.1%) than with placebo (-3.1%). This resulted in a statistically significant relative reduction from baseline in UPCR for the atrasentan (Vanrafia), corresponding to a 36% relative reduction with atrasentan (Vanrafia) (P < 0.001).

- XIII. Proteinuria reduction was evident at week 6 and sustained through week 36. This treatment effect at Week 36 was also consistent in the exploratory SGLT2i cohort. Exploratory efficacy endpoints for changes in UPCR from baseline to Week 36 in the SGLT2i cohort was -39.6% for atrasentan (Vanrafia) (14 patients) compared to -3.4% for placebo (15 patients). This corresponds to a relative reduction of 37.4% in UPCR from baseline.
- XIV. The expected place in therapy for atrasentan (Vanrafia) is as an adjunct to supportive care that includes renin-angiotensin system inhibitor (RASi) with or without an SGLT2i for patients at high risk of IgAN progression based on sustained proteinuria.
- XV. The safety profile of atrasentan (Vanrafia) was consistent with other endothelin receptor antagonist (ERA) therapies. The most common adverse events (vs. placebo) included peripheral edema (24% vs. 10%), nasopharyngitis (18% vs. 12%), headache (14% vs. 8%), fatigue (13% vs. 7%), and anemia (11% vs. 6%). Adverse events of special interest in the treatment group included anemia, fluid retention, and vasodilation or hypotension. Permanent discontinuation due to AEs occurred in 7% of patients. Dose interruption occurred in 16% of patients on atrasentan (Vanrafia). Atrasentan (Vanrafia) carries a black box warning for embryo-fetal toxicity and warnings and precautions for hepatotoxicity, fluid retention, and decreased sperm count.
- XVI. The quality of evidence for atrasentan (Vanrafia) is considered low. The ALIGN clinical program consists of an ongoing trial, alluding to a short-term indication of efficacy. Reduction in proteinuria < 1 g/day is an objective surrogate marker for IgAN. However, it falls shy of predicting long-term patient outcomes such as progression to ESRD, dialysis dependence and overall mortality in ESRD. The Kidney Health Initiating workgroup and National Kidney Foundation recommend the use of dual (primary and confirmatory) endpoints of proteinuria reduction as well as slope of eGFR decline. At this time, effect of atrasentan (Vanrafia) on eGFR is unknown compared to other agents on the market. Currently, all four approved therapies for IgAN demonstrate comparable reductions in UPCR; but ultimately, confirmatory eGFR data from both iptacopan (Fabhalta) and atrasentan (Vanrafia) will be essential for evaluating their impact on kidney function.
- XVII. As of July 2025, no clinical trials support the combined use of multiple novel therapies in IgAN. While it is known that multiple pathophysiologic mechanisms contribute to kidney function loss in patients with IgAN, particularly those at risk of progressive decline, targeting these mechanisms concurrently may be necessary. In clinical practice, this could mean combining standard of care therapies with one or more agents. In the absence of updated clinical guidelines and supporting evidence to allow combination use of IgAN therapies (e.g., atrasentan

- (Vanrafia), budesonide (Tarpeyo), sparsentan (Filspari), iptacopan (Fabhalta), etc.), concurrent use is contraindicated and considered experimental and investigational.
- XVIII. During the PROTECT and ALIGN clinical trials, patients with an eGFR ≤ 30 mL/min/1.73m², patients on dialysis, and history of kidney transplant were excluded from participation. Efficacy and safety of sparsentan (Filspari) and atrasentan (Vanrafia) in this selected population has not been evaluated and is therefore considered experimental and investigational.

Investigational or Not Medically Necessary Uses

- I. Sparsentan (Filspari) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below. There are currently ongoing trials in the setting of focal segmental glomerulosclerosis (FSGS). However, no data is available to support efficacy and safety of sparsentan (Filspari) for the treatment of FSGS:
 - A. Secondary IgA nephropathy
 - B. Newly diagnosed IgAN without high risk of disease progression
 - C. IgAN-treatments in combination (budesonide (Tarpeyo) atrasentan (Vanrafia), sparsentan (Filspari), iptacopan (Fabhalta), etc.)
 - D. Focal segmental glomerulosclerosis (FSGS)
 - E. Chronic kidney disease (CKD) other than primary IgAN

References

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
budesonide (Tarpeyo)	Primary IgA nephropathy; at high risk of progression
Fabhalta: Proximal Complement Inhibitors	Primary IgA nephropathy; at high risk of progression

Policy Implementation/Update

Action and Summary of Changes	Date
Addition of atrasentan (Vanrafia) to policy. Updated initial and renewal criteria to exclude the use of IgAN therapies in combination, exclude use in dialysis and kidney transplant, include eGFR, remove use of corticosteroid requirement, and clarified use of RASi with Vanrafia. Updated E/I, supporting evidence, references, and related policies.	08/2025
Policy created	05/2023

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP311

Description

Spesolimab SC (Spevigo) is an IL-36 receptor antagonist that is administered subcutaneously.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
spesolimab SC (Spevigo)	Generalized pustular psoriasis (GPP), when not experiencing a flare	150 mg/mL pre-filled syringe	2 mL/28 days

Initial Evaluation

- I. **Spesolimab SC (Spevigo)** may be considered medically necessary when the following criteria are met:
 - A. Member is 12 years of age or older; **AND**
 - B. Medication is prescribed by, or in consultation with, a dermatologist; **AND**
 - C. Medication will not be used in combination with any of the following:
 1. Systemic immunomodulators (e.g., retinoids); **AND**
 2. Systemic immunosuppressants (e.g., cyclosporine, methotrexate, etc.); **AND**
 3. Biologic agents [e.g., Taltz (ixekizumab), Siliq (brodalumab), Stelara (ustekinumab), Skyrizi (risankizumab), Cimzia (certolizumab), Simponi (golimumab), etc.]; **AND**
 4. Other non-biologic specialty agents [e.g., Xeljanz (tofacitinib), Olumiant (baricitinib), Rinvoq (upadacitinib), etc.]; **AND**
 - D. Documentation member weighs at least 40 kg; **AND**
 - E. Documentation member has a diagnosis of **generalized pustular psoriasis (GPP)**; **AND**
 - F. Provider attestation medication is intended for use of generalized pustular psoriasis (GPP) flare prevention; **AND**
 - G. Provider attestation member has experienced at least one generalized pustular psoriasis (GPP) flare
- II. Spesolimab SC (Spevigo) is considered investigational when used for all other conditions, including but not limited to:
 - A. Pyoderma gangrenosum
 - B. Palmoplantar pustulosis
 - C. Crohn's disease
 - D. Hidradenitis suppurativa
 - E. Ulcerative colitis

- F. Atopic eczema
- G. Netherton syndrome
- H. Plaque psoriasis

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Documentation that member has exhibited improvement or stability of disease symptoms [e.g., reduction in flares, improved quality of life] **AND**
- IV. Medication will not be used in combination with any of the following:
 - A. Systemic immunomodulators (e.g., retinoids); **AND**
 - B. Systemic immunosuppressants (e.g., cyclosporine, methotrexate, etc.); **AND**
 - C. Biologic agents [e.g., Taltz (ixekizumab), Siliq (brodalumab), Stelara (ustekinumab), Skyrizi (risankizumab), Cimzia (certolizumab), Simponi (golimumab), etc.]; **AND**
 - D. Other non-biologic specialty agents [e.g., Xeljanz (tofacitinib), Olumiant (baricitinib), Rinvoq (upadacitinib), etc.]

Supporting Evidence

- I. Generalized pustular psoriasis (GPP) is a rare subtype of psoriasis that can develop independently or in association with pre-existing psoriasis. Generalized pustular psoriasis (GPP) differs from other forms of psoriasis because it presents as widespread skin plaques with pustules surrounded by erythematous skin with intense itching and/or pain throughout the body. Generalized pustular psoriasis (GPP) flares are often accompanied by systemic symptoms (e.g., high fever, chills, rapid pulse, fatigue, nausea, etc.) and may lead to hospitalizations. The duration of these flares varies, lasting for a few weeks to a few months before spontaneously clearing and remaining latent until re-exposure to a precipitating factor or for unknown reasons. Currently, GPP is diagnosed by provider assessments since there is no scoring tool or rubric that is used clinically. Historically, GPP is treated with off-label systemic immunomodulators, systemic immunosuppressants, biologics, and other non-biologic specialty agents. However, off-label treatments are supported by low-quality evidence (e.g., case reports, single arm open-label trials). Spesolimab SC (Spevigo) is the first medication to receive a specific indication for the treatment of GPP when not experiencing a flare (i.e., for flare prevention). The goal of treatment is to improve quality of life by minimizing the recurrence of flares to reduce complications, hospitalizations, morbidity, and mortality associated with GPP.
- II. Treatment with spesolimab (Spevigo) is considered medically necessary in those 12 years of age and older. This requirement is supported by Effisayil 2, the pivotal clinical trial that evaluated the safety and efficacy of spesolimab SC (Spevigo). This trial enrolled patients 12 years of age and older weighing at least 40 kg. In addition, the FDA-approved label requirement is also in those 12 years of age and older when used in treatment of GPP when not experiencing a flare. Per the package insert, pharmacokinetic analyses show similar drug exposure levels in adults

and pediatric patients 12 years of age and older and weighing 40 kg or more. Due to uncertainties regarding adolescent organ development and ability to clear or metabolize spesolimab SC (Spevigo), current data does not support use of this product in members younger than 12 years of age.

- III. Given the rarity and complexity of GPP, diagnosis and therapy choices should be directed by a specialist such as a dermatologist.
- IV. Spesolimab SC (Spevigo) has not been adequately studied in combination with other off-label therapies used for the treatment of GPP. Participants in the Effisayil 2 trial were required to discontinue systemic and topical GPP therapy prior to or at randomization. However, the guidelines do support topical medications as adjunctive treatment options. Even though the use of spesolimab SC (Spevigo) in combination with topical medications hasn't been studied, there is less concern with them being used together due to lower systemic absorption with topical drugs and guideline support as adjunctive treatments. On the other hand, systemic immunomodulators, systemic immunosuppressants, biologics, and other non-biologic specialty agents pose a concern regarding safety due to additive systemic effects and drug-drug interactions. Thus, their use in combination with spesolimab SC (Spevigo) is considered experimental and investigational at this time.
- V. A consensus statement from the National Psoriasis Foundation (NPF) states the diagnosis of GPP is made based on the assessment of clinical features such as recurrent episodes of disseminated, sterile, monomorphic pustules on a background of widespread erythema. The NPF states skin biopsy is not required for the diagnosis of GPP because histologic features may be nonspecific, and it may delay treatment. The NPF further states GPP phenotype classification criteria are informative for clinical trials, but it should not be used to deny or delay treatment in clinical practice.
- VI. Spesolimab (Spevigo) has different routes of administration. It is available as a subcutaneous (SC) and an intravenous (IV) formulation. The FDA-approved indication and dosing is different for each dosage form. Spesolimab SC (Spevigo) is FDA-approved for the prevention of GPP flares; while, spesolimab IV (Spevigo) is FDA-approved for the treatment of GPP flares.
- VII. The study population in the Effisayil 2 trial included patients that had at least two past GPP flares. Generalized pustular psoriasis (GPP) flares are difficult to diagnose; thus, having two previous GPP flares helped identify true flare episodes in the pivotal trial. There is uncertainty in the benefit provided by spesolimab SC (Spevigo) for those with a history of one previous flare as this patient population has not been adequately studied and may not be representative of a patient population in need of preventative treatment. However, given the potential severe complications associated with each GPP flare (e.g., renal, hepatic, respiratory, or heart failures, etc.), history of one past GPP flare may be adequate to support medical necessity for preventative use. While there is a lack of literature regarding the incidence and timing of GPP flare recurrence, the information that is available suggests patients with GPP experience one flare every couple of years. There are multiple retrospective studies with follow-up data extending out as long as five years that suggest most patients experience at least one flare during that time frame.
- VIII. The American Academy of Dermatology (AAD) and National Psoriasis Foundation (NPF) guidelines for the management of psoriasis with biologics (2019) and systemic non-biologic therapies (2020) recommend cyclosporine, ixekizumab (Taltz), and brodalumab (Siliq)

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specifically for the treatment of generalized pustular psoriasis (strength of recommendation grade B with a level of evidence I-II, meaning the recommendation was based on good, inconsistent, or limited-quality patient-oriented evidence). The evidence supporting use of these therapies is of low-quality as the information and data come primarily from case reports and/or single arm, open-label trials.

Investigational or Not Medically Necessary Uses

- I. Spesolimab SC (Spevigo) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Pyoderma gangrenosum
 - i. Spesolimab SC (Spevigo) is currently under investigation for the treatment of pyoderma gangrenosum in a Phase 2, open-label, single group assignment trial designed to evaluate change in global pyoderma gangrenosum (GPG) severity score in male or females subject ≥ 18 years of age with clinical diagnosed ulcerative pyoderma gangrenosum with PARACELSUS score ≥ 10 . Primary completion is expected in September 2025. Requests for this indication are considered experimental and investigational at this time.
 - B. Palmoplantar pustulosis
 - i. There is currently no active trial evaluating the use of spesolimab SC (Spevigo) in patients with palmoplantar pustulosis. There is insufficient evidence to support the safety and efficacy of spesolimab SC (Spevigo) in this disease space. Requests for this indication are considered experimental and investigational at this time.
 - C. Crohn's disease
 - i. There is currently no active trial evaluating the use of spesolimab SC (Spevigo) in patients with Crohn's disease. There is insufficient evidence to support the safety and efficacy of spesolimab SC (Spevigo) in this disease space. Requests for this indication are considered experimental and investigational at this time.
 - D. Hidradenitis suppurativa
 - i. Spesolimab SC (Spevigo) is currently under investigation for the treatment of hidradenitis suppurativa. There are multiple trials currently recruiting (estimated primary completion 2024-2030) as well as several trials that have been completed with results yet to be posted. Requests for this indication are considered experimental and investigational at this time.
 - E. Ulcerative colitis, Atopic eczema
 - i. There is currently no active trial evaluating the use of spesolimab SC (Spevigo) in patients with ulcerative colitis or atopic eczema. There is insufficient evidence to support the safety and efficacy of spesolimab SC (Spevigo) in this disease space. Requests for this indication are considered experimental and investigational at this time.
 - F. Netherton syndrome
 - i. Spesolimab SC (Spevigo) is currently under investigation for the treatment of Netherton syndrome in a phase 2/3, randomized, parallel assignment, placebo-controlled, double-blinded trial designed to measure ichthyosis area severity index (IASI) response in male or female patients ≥ 12 years of age and ≥ 35 kg in

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weight with a diagnosis of Netherton syndrome. Primary completion is expected in December 2024. Requests for this indication are considered experimental and investigational at this time.

G. Plaque psoriasis

- i. There is currently no active trial evaluating the use of spesolimab SC (Spevigo) in patients with plaque psoriasis. There is insufficient evidence to support the safety and efficacy of spesolimab SC (Spevigo) in this disease state. Requests for this indication are considered experimental and investigational at this time.

Appendix

- I. Dosing regimens of spesolimab SC (Spevigo) in members 12 years of age and older and weighing at least 40 kg:
 - A. Initiating spesolimab SC (Spevigo) for the first time
 1. 600 mg SC (4 x 150 mg injections) loading dose followed by 300 mg SC (2 x 150 mg injections) 4 weeks later and every 4 weeks thereafter
 - B. Initiating or reinitiating spesolimab SC (Spevigo) following treatment of a GPP flare with spesolimab IV (Spevigo)
 1. 300 mg SC (2 x 150 mg injections) 4 weeks after treatment of the flare and every 4 weeks thereafter
 2. A subcutaneous loading dose is not required following treatment of a GPP flare with spesolimab IV (Spevigo)

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3. Menter A, Gelfand JM, Connor C, et al. Joint American Academy of Dermatology-National Psoriasis Foundation guidelines of care for the management of psoriasis with systemic nonbiologic therapies. *J Am Acad Dermatol*. 2020;82(6):1445-1486. doi:10.1016/j.jaad.2020.02.044
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13. UpToDate. Pustular psoriasis: Management. 2022. Updated October 21, 2022. Accessed August 5, 2024.
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Related Policies

Currently there are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	11/2024

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP318

Description

Stiripentol (Diacomit) is an orally administered anticonvulsant with direct effects mediated through the GABA_A receptor.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
stiripentol (Diacomit)	Dravet Syndrome	250 mg capsules	180 capsules/30 days
		500 mg capsules	
		250 mg powder for oral suspension	180 packets/30 days
		500 mg powder for oral suspension	

Initial Evaluation

- I. **Stiripentol (Diacomit)** may be considered medically necessary when the following criteria below are met:
 - A. Member is 6 months of age or older; **AND**
 1. Member weighs at least 7 kg (15 lbs); **AND**
 - B. Medication is prescribed by or in consultation with a neurologist; **AND**
 - C. Medication will not be used as monotherapy (i.e., will be used in combination with another antiepileptic agent); **AND**
 - D. A diagnosis of **Dravet Syndrome** when the following are met:
 - i. Treatment with clobazam (Onfi) and valproate (Depakote) has been ineffective, contraindicated, or not tolerated; **AND**
 - ii. Medication will be used in combination with clobazam (Onfi)
- II. Stiripentol (Diacomit) is considered investigational when used for all other conditions, including but not limited to:
 - A. Epileptic encephalopathies associated with SCN1A mutations
 - B. Pharmacoresistant Focal Seizures
 - C. Other non-FDA approved seizure disorder
 - D. Primary Hyperoxaluria
 - E. When used as monotherapy

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Member has exhibited improvement or stability of disease symptoms [e.g., reduction in seizure frequency, seizure duration, incidence of ER visits or hospitalization due to seizure, etc.]; **AND**
- IV. Medication will be used in combination with clobazam (Onfi)

Supporting Evidence

- I. Dravet syndrome, previously known as severe myoclonic epilepsy in infancy, is a rare pediatric genetic epilepsy syndrome that typically presents within the first year of life (infancy) and is characterized by refractory epilepsy and neurodevelopmental problems. It can be difficult to diagnose, with common misdiagnoses including Lennox-Gastaut syndrome, cerebral palsy and vaccine encephalopathy. Because Dravet syndrome is generally treatment refractory, with high-touch care and monitoring required, stiripentol (Diacomit) must be prescribed by, or in consultation with a neurologist.
- II. The use of stiripentol (Diacomit) has not been studied as monotherapy, and FDA labeling notes that there are no clinical data to support the use of stiripentol (Diacomit) as monotherapy. Therefore, if a member has a contraindication to therapy with clobazam, then another antiepileptic agent will be required to be used in combination with stiripentol (Diacomit).
- III. Stiripentol (Diacomit) was studied in two Phase III, multicenter, randomized, placebo-controlled trials in 64 patients between the ages of three and 18 years who have been diagnosed with Dravet syndrome with previous inadequately controlled seizures on clobazam and valproate. Patients received stiripentol (Diacomit) as add-on therapy to on-going use of clobazam and valproate. The primary efficacy endpoint was responder rate, defined as a patient who experienced a >50% decrease in the frequency (per 30 days) of generalized clonic or tonic-clonic seizures, which was statistically significant for stiripentol (Diacomit) compared to placebo in both studies.
- IV. The effectiveness of stiripentol (Diacomit) for patients aged six months to less than three years of age was extrapolated from the demonstration of effectiveness in patients aged three years to less than 18 years of age in the trials pivotal trials described above (supporting evidence I).
- V. Although stiripentol (Diacomit) was studied in combination with both clobazam and valproate, the FDA indication is for the treatment of seizures associated with Dravet syndrome in patients taking clobazam. Pharmacokinetic data from the clinical trial revealed that the serum levels of both clobazam and its active component, norclobazam, were increased substantially with stiripentol (Diacomit), while the serum levels of valproate were unchanged. Because the relative contribution of efficacy of the increased levels of clobazam and norclobazam with stiripentol (Diacomit) treatment remains incompletely defined, along with concerns for long-term

teratogenicity and side effects of valproate, the FDA concluded that stiripentol (Diacomit) will be indicated in patients taking clobazam only.

- VI. The NICE guidelines for Dravet syndrome recommend valproate as first-line therapy, then clobazam, and stiripentol (Diacomit) as adjunct first-line therapy. Cannabidiol (Epidiolex), in combination with clobazam, and fenfluramide (Fintepla) can also be considered as second-line add-on therapy. In addition to these guidelines, the international consensus on diagnosis and treatment of Dravet syndrome recommend first-line treatment with valproate, second-line with stiripentol (Diacomit), clobazam, or fenfluramine (Fintepla), and third-line with cannabidiol (Epidiolex).

Investigational or Not Medically Necessary Uses

- I. Stiripentol (Diacomit) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
- A. Epileptic encephalopathies associated with SCN1A mutations
 - B. Pharmacoresistant Focal Seizure
 - C. Other non-FDA approved seizure disorder
 - D. Primary hyperoxaluria
 - E. When used as monotherapy
 - i. Stiripentol (Diacomit) has not been studied as monotherapy in Dravet syndrome. Package label also notes lack of clinical data to support the use as monotherapy.

References

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy

Policy Name	Disease state
cannabidiol (Epidiolex)	Lennox-Gastaut syndrome Dravet syndrome Tuberous Sclerosis Complex
fenfluramine (Fintepla)	Dravet syndrome Lennox-Gastaut syndrome

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated formatting of policy and quantity limit table; updated age requirement to 6 months and older; removed requirement for combination use with valproate from initial criteria; removed concomitant use with cannabidiol (Epidiolex) from E/I section	09/2022
Policy created	05/2019

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP154

Split Fill Management*

Description

Sunitinib (Sutent) is an orally administered tyrosine kinase inhibitor targeting multiple receptors.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
sunitinib malate (generic Sutent)	12.5 mg capsule	Gastrointestinal stromal tumor	28 capsules/42 days for all indications except neuroendocrine pancreatic tumor
	25 mg capsule	Renal cell carcinoma, adjuvant following nephrectomy	
	37.5 mg capsule	Renal cell carcinoma, advanced	28 capsules/28 days for pancreatic neuroendocrine tumor
	50 mg capsule	Neuroendocrine pancreatic tumor	
sunitinib (Sutent)	12.5 mg capsule	Gastrointestinal stromal tumor	28 capsules/42 days for all indications except neuroendocrine pancreatic tumor
	25 mg capsule	Renal cell carcinoma, adjuvant following nephrectomy	
	37.5 mg capsule	Renal cell carcinoma, advanced	28 capsules/28 days for pancreatic neuroendocrine tumor
	50 mg capsule	Neuroendocrine pancreatic tumor	

Initial Evaluation

- I. **Sunitinib (Sutent)** may be considered medically necessary when the following criteria below are met:
 - A. Member is 18 years of age or older; **AND**
 - B. Medication is prescribed by, or in consultation with, an oncologist; **AND**
 - C. Sunitinib (Sutent) will be used as monotherapy; **AND**
 - D. The request is for generic sunitinib malate; **OR**
 1. The request is for brand Sutent and treatment with generic sunitinib malate is contraindicated or not tolerated; **AND**
 - E. A diagnosis of one of the following:
 1. **Gastrointestinal stromal tumor (GIST); AND**

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- i. Treatment with generic imatinib or brand imatinib (Gleevec) has been ineffective, contraindicated, or not tolerated; **OR**
 - 2. **Pancreatic neuroendocrine tumor (pNET); AND**
 - i. The member has unresectable, locally advanced (stage III), or metastatic (stage IV) disease; **OR**
 - 3. **Renal cell carcinoma (RCC); AND**
 - i. Disease is advanced (stage III) or metastatic (stage IV)
- II. Sunitinib (Sutent) is considered not medically necessary when criteria above are not met and/or when used for:
 - A. Adjuvant treatment for renal cell carcinoma
- III. Sunitinib (Sutent) is considered investigational when used for all other conditions, including but not limited to:
 - A. Angiosarcoma
 - B. Breast cancer
 - C. Colorectal cancer
 - D. Central nervous system cancers
 - E. Neuroendocrine tumors other than those of pancreatic origin
 - F. Gastric cancer
 - G. Lung cancer
 - H. Soft tissue sarcoma
 - I. Thyroid carcinoma
 - J. Osteosarcoma
 - K. Cholangiocarcinoma
 - L. Adenoid cystic carcinoma

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. The request is for generic sunitinib malate; **OR**
 - A. The request is for brand Sutent and treatment with generic sunitinib malate is contraindicated or not tolerated; **AND**
- IV. Sunitinib (Sutent) will be used as monotherapy; **AND**
- V. Disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread

Supporting Evidence

- I. Sunitinib (Sutent) was evaluated for gastrointestinal stromal tumor (GIST) in a randomized, double-blind, placebo-controlled trial in adults that had previously progressed on imatinib (Gleevec) or were intolerant to therapy. Outcomes included time-to-tumor progression (TTP), progression-free survival (PFS), and objective response rate (ORR) and were statistically significant in favor of sunitinib (Sutent). At the time of disease progression, treatment was unblinded and those originally on placebo were allowed to crossover to open-label sunitinib (Sutent). At the final analysis overall survival (OS) was not statistically different between the treatment arms.
- II. A second study of sunitinib (Sutent) for GIST was conducted as an open-label, single-arm trial in adults that had previously progressed on, or had intolerance to, imatinib (Gleevec). Five of the 55 subjects included had a partial response to therapy (9.1%, CI 3-20%).
- III. For renal cell carcinoma (RCC), sunitinib (Sutent) was evaluated in a randomized trial versus IFN- α in treatment-naïve RCC. The outcomes evaluated were PFS and ORR, both of which were statistically significant in favor of sunitinib (Sutent).
- IV. In the adjuvant treatment setting for RCC, sunitinib (Sutent) was evaluated in a randomized, double-blind, placebo-controlled trial adults with high risk of recurrence following nephrectomy. Subjects were required to have clear cell histology. Subjects were treated for nine cycles maximum. The primary outcome was disease-free survival (DFS) which was statistically significant in favor of sunitinib (Sutent). Overall survival was a secondary endpoint; however, data was not mature at time of analysis and the medication is associated with a significant safety profile.
- V. For pancreatic neuroendocrine tumors (pNET), sunitinib (Sutent) was evaluated in a randomized, double-blind, placebo-controlled trial in adults with unresectable disease. The Independent Data Monitoring Committee was terminated early which may have led to an overestimate of the PFS. The outcomes of PFS and ORR were statistically significant in favor of sunitinib (Sutent); however, OS data was not mature at time of analysis. In a follow up analysis at five years a statistical significant different in OS was not demonstrated; however, this may have been confounded by crossover.
- VI. Sunitinib has not been evaluated for safety and/or efficacy in pediatric patients. The dosing for sunitinib (Sutent) outside of pancreatic neuroendocrine tumors, is four weeks on two weeks off. A maximum of nine 6-week cycles of therapy for adjuvant RCC has been evaluated and FDA-approved for adjuvant RCC. This is approximately 13 months of therapy total.

Investigational or Not Medically Necessary Uses

- I. Adjuvant treatment for renal cell carcinoma
 - A. Following one year of treatment with sunitinib (Sutent), patients experienced a 1-year improvement in disease free survival compared to placebo; however, there was no improvement in overall survival. Sunitinib (Sutent) is associated with significant toxicity and patients experienced a decline in quality of life while on treatment compared to placebo. NCCN has listed adjuvant sunitinib (Sutent) as a Category 3 recommendation, as there is still no clear role for adjuvant systemic therapy in this setting. Observation or

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clinical trials are still considered the standard of care given the lack of clinically meaningful supportive data for systemic therapy in the adjuvant setting.

II. Sunitinib (Sutent) has not been sufficiently studied for safety or efficacy and/or is currently being evaluated in clinical trials for the following indications:

- A. Angiosarcoma
- B. Breast cancer
- C. Colorectal cancer
- D. Central nervous system cancers
- E. Neuroendocrine tumors other than those of pancreatic origin
- F. Gastric cancer
- G. Lung cancer
- H. Soft tissue sarcoma
- I. Thyroid carcinoma
- J. Osteosarcoma
- K. Cholangiocarcinoma
- L. Adenoid cystic carcinoma

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

References

1. Sutent [Prescribing Information]. New York, NY. Pfizer Labs. May 2019.
2. Demetri GD, Van oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *Lancet*. 2006;368(9544):1329-38.
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Policy Implementation/Update:

Action and Summary of Changes	Date
Addition of trial and failure of generic sunitinib prior to use of branded Sutent. Addition of monotherapy requirements evaluated upon renewal. Updated initial approval duration from three months to six months.	09/2021
Prior authorization criteria transitioned to policy format. Addition of age edit, monotherapy requirements, and clarification of renal cell carcinoma uses.	11/2019
Review of adjuvant RCC setting	01/2018
Policy created	03/2012

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Policy Type: PA/SP

Pharmacy Coverage Policy: UMP246

Description

These agents target the JAK/STAT (janus associated kinase/signal transducer and activator of transcription) pathway that involves proteins, cytokines, and other inflammatory mediators that lead to immune activation and inflammation in chronic inflammatory disease states. The purpose of this policy is to ensure the appropriate use of these agents.

Length of Authorization

- Initial: Six months
- Renewal:
 - i. Upadacitinib (Rinvoq) 45 mg XR tablet: No renewal
 - ii. All other medications: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit*
abrocitinib (Cibinqo™)	Atopic Dermatitis (AD)	100 mg tablet	30 tablets/30 days
		200 mg tablet	
baricitinib (Olmiant®)	Rheumatoid Arthritis (RA)	1 mg tablet	30 tablets/30 days
		2 mg tablet	
	Alopecia areata	2 mg tablet	30 tablets/30 days
		4 mg tablet	
	COVID-19†	4 mg tablet	N/A
deucravacitinib (Sotyktu™)	Plaque Psoriasis	6 mg tablet	30 tablets/30 days
deuruxolitinib (Leqselvi)	Alopecia areata	8 mg tablets	60 tablets/30 days
ritlecitinib (Litfulo)	Alopecia areata	50 mg capsules	28 capsules/28 days
upadacitinib (Rinvoq™)	Rheumatoid Arthritis (RA) Ankylosing spondylitis (AS) Non-radiographic axial spondyloarthritis (nr- axSpA) Giant Cell Arteritis (GCA)	15 mg XR tablet	30 tablets/30 days
	Atopic Dermatitis (AD)	15 mg XR tablet	30 tablets/30 days
		30 mg XR tablet	
	Ulcerative Colitis (UC) Crohn's Disease (CD)	15 mg XR tablet	30 tablets/30 days
		30 mg XR tablet	
	Polyarticular Juvenile Idiopathic Arthritis (PJIA) Psoriatic arthritis (PsA)	45 mg XR tablet	28 tablets/28 days
		1mg/ mL oral solution (180ml bottle)	Weight-based dosing: • 10 kg -20 kg: 1 bottle/ 30 days

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			20 kg – 30 kg: 1 bottle/ 22 days 30 kg and over: 1 bottle/ 15 days
		15 mg XR tablet	Body weight ≥30 kg: 30 tablets/30 days**
tofacitinib (Xeljanz®)	Ankylosing spondylitis (AS) Rheumatoid Arthritis (RA) Psoriatic Arthritis (PsA)	5 mg tablet	60 tablets/ 30 days
		11mg XR tablet	30 tablets/30 days
	Polyarticular Juvenile Idiopathic Arthritis (PJIA)	1mg/mL oral solution (240ml bottle)	Weight-based dosing: 10 kg-20 kg: 1 bottle/30 days 20 kg-40 kg: 1 bottle/30 days - Body weight ≥40 kg: 1 bottle/24 days
		5 mg tablet	Body weight ≥40 kg: 60 tablets/30 days**
	Ulcerative Colitis (UC)	5 mg tablet	60 tablets/30 days
		10 mg tablet	
		11 mg XR tablet	30 tablets/30 days
		22 mg XR tablet	

*Lower doses may be used in renal and/or hepatic impairment, lymphopenia, neutropenia, anemia, strong CYP3A4 inhibitors (e.g., ketoconazole), strong CYP2C19 inhibitor(s) (e.g., fluconazole)

** Dosing for PJIA is based on body weight. Patients with body weight greater than ≥40kg on the oral solution may be switched to Xeljanz 5 mg tablets or greater than ≥ 30kg may move to Rinvoq XR 15mg tablets.

† Use of baricitinib (Olumiant) in the COVID-19 setting is indicated in hospitalized adults only. Per FDA label dosing is for 14 days or until hospital discharge, whichever occurs first. Review of coverage falls within the medical benefit and is excluded from the pharmacy benefit for this indication.

Applicable to All Disease States and Treatment Options Listed Below

- I. Contraindication to one preferred treatment option listed in the policies below does not exempt the requirement to try another required agent prior to biologic approval. For instance, in the rheumatoid arthritis requirements to follow, a contraindication to methotrexate but not to other available treatment options (sulfasalazine, hydroxychloroquine, leflunomide, etc.) would not satisfy criteria I(C)(1). In other words, a member would still need to try at least one of these other agents as clinically appropriate.
- II. Approved treatments are not to be used in combination with other biologics or other non-biologic specialty medications used to treat autoimmune conditions. Use of tumor necrosis factor (TNF) blockers such as adalimumab in combination with other biologics, such as anakinra or abatacept, has demonstrated and increased risk of serious infection with insufficient evidence for added benefit. Per product labeling, use of JAK inhibitors with concomitant biologics or with potent immunosuppressants such as azathioprine and cyclosporine are not recommended as there is insufficient data to support their use as dual therapy. Likewise, sufficient data is not currently available to support the safety and efficacy of apremilast use in combination with other agents listed in this policy.

Rheumatoid Arthritis

- I. **Upadacitinib (Rinvoq) or tofacitinib (Xeljanz/Xeljanz XR)** may be considered medically necessary when the following criteria below are met:

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- A. Member is being managed by, or in consultation with, a rheumatologist; **AND**
 - B. A diagnosis of **rheumatoid arthritis** when the following are met:
 - 1. Treatment with an oral, non-biologic, non-specialty disease-modifying antirheumatic drug (DMARD) has been ineffective or not tolerated, or all are contraindicated (e.g., guidelines direct to methotrexate, sulfasalazine, hydroxychloroquine, or leflunomide. Other examples include azathioprine and cyclosporine.); **AND**
 - C. Treatment with one or more tumor necrosis factor (TNF) blockers [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], etanercept (Enbrel) etc.] has been ineffective, not tolerated, or contraindicated.
- II. **Baricitinib (Olumiant)** may be considered medically necessary when the following criteria below are met:
- A. Criteria I(A)-I(B) above are met; **AND**
 - B. Treatment with adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], etanercept (Enbrel), tocilizumab-aazg (Tyenne), upadacitinib (Rinvoq), and tofacitinib (Xeljanz/Xeljanz XR) have been ineffective, contraindicated, or not tolerated.

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Member has exhibited improvement or stability of disease symptoms; **AND**
- IV. The medication prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat rheumatoid arthritis or another auto-immune condition (e.g., Otezla/Otezla XR, Remicade, etc.).

Supporting Evidence

- I. The agents listed above are approved for adult patients with rheumatoid arthritis (RA) that had an inadequate response or intolerance to TNF inhibitors based on safety and efficacy data from randomized-controlled trials.
- II. The 2021 American College of Rheumatology (ACR) guidelines for rheumatoid arthritis address the use of conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), targeted-synthetic DMARDs (tsDMARDs) such as JAK inhibitors, and biologic DMARDs (bDMARDs) as TNF inhibitors and non-TNF inhibitors. A majority of recommendations are based on low or very low certainty of evidence.
 - The 2021 ACR guidelines strongly recommend the use of csDMARD monotherapy (methotrexate preferred) in patients who are DMARD-naïve with moderate-to-severe RA. Recommended csDMARDs include methotrexate, sulfasalazine, hydroxychloroquine, and leflunomide. Despite moderate evidence in the SELECT-EARLY study noting higher efficacy of upadacitinib over methotrexate in DMARD-naïve patients with moderate-to-severe RA, there is limited long-term safety data to strongly recommend the use of tsDMARDs (e.g., JAK inhibitors) as first line therapy. Therefore, methotrexate monotherapy remains the preferred first-line therapy over

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tsDMARDs in DMARD-naïve patients based on established safety and efficacy. Additionally, JAK inhibitors are not FDA approved for use in csDMARD-naïve patients.

- For patients who are DMARD-naïve with low disease activity, initial trial of hydroxychloroquine over other csDMARDs, and sulfasalazine over methotrexate is conditionally recommended.
 - For DMARD-naïve patients with moderate-to-severe disease activity, methotrexate monotherapy is conditionally recommended over methotrexate in combination with a TNF inhibitor due to low-certainty evidence with combination use. The recommendation is conditional because patients with poor prognostic factors may benefit from a faster onset of action and greater change of improvement with dual therapy.
 - In DMARD-naïve patients with moderate-to-severe disease activity, methotrexate monotherapy is strongly recommended over the addition of a non-TNF inhibitor or tsDMARD based additional risks of adding a biologic or tsDMARD and low-quality data evaluating superiority over methotrexate monotherapy.
 - For patients with moderate-to-severe disease activity despite adequate trial of csDMARD monotherapy, a treat-to-target approach is strongly recommended and the addition of a bDMARD or tsDMARD is conditionally recommended as combination therapy may provide a more rapid treatment response. The recommendation was based on very low certainty of evidence.
 - The guidelines conditionally recommend switching to a bDMARD or tsDMARD of a different class over switching to a bDMARD or tsDMARD belonging to the same class for patients taking a bDMARD or tsDMARD who are not at target, however the recommendation is based on very low-quality evidence supporting greater improvement in disease activity among patients switching therapy classes. There are no current recommendations for using a bDMARD over a tsDMARD, however patients and providers should engage in a shared decision-making approach based on the available safety data of JAK inhibitors.
 - The 2021 ACR guidelines have additional recommendations for patient specific populations, including patients with co-morbid heart failure, lymphoproliferative disorder, Hepatitis B infection, nonalcoholic fatty liver disease (NAFLD), persistent hypogammaglobulinemia without infection, and populations with history of serious infection(s).
- III. The 2019 European League Against Rheumatism (EULAR) guidelines follow similar recommendations to the 2021 ACR guidelines, and state that patients with highly active RA despite treatment with csDMARDs may receive a bDMARD or JAK inhibitor based on high level of evidence. Biologic DMARDs (TNF-inhibitors, IL-6 inhibitors, etc.) were previously recommended over JAK inhibitors, but newer data comparing JAK inhibitors to adalimumab failed to demonstrate clinically relevant endpoints favoring bDMARDs over JAK inhibitors.
- IV. There are currently no head-to-head trials comparing the safety and efficacy of Xeljanz, Rinvoq, or Olumiant in patients with rheumatoid arthritis.

References

1. Fraenkel L, Bathon JM, England BR, et al. 2021 American college of rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Care Res.* 2021;73(7):924-939.
2. Alten R, Mischkewitz M. 2021 ACR guideline reflects changes in RA treatment. *Nat Rev Rheumatol.* 2021;17(9):513-514. doi:10.1038/s41584-021-00667-2

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3. Van Vollenhoven, R. et al. Efficacy and safety of upadacitinib monotherapy in methotrexate-naïve patients with moderately-to-severely active rheumatoid arthritis (SELECT-EARLY): a multicenter, multi-country, randomized, double-blind, active-comparator-controlled trial. *Arthritis Rheumatol.* 72, 1607–1620 (2020)
4. UpToDate, Inc. General principles and overview of management of rheumatoid arthritis in adults . UpToDate [database online]. Waltham, MA. Last updated October 18, 2021. Available at: <http://www.uptodate.com/home/index.html>.
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6. Wang F, Sun L, Wang S, et al. Efficacy and Safety of Tofacitinib, Baricitinib, and Upadacitinib for Rheumatoid Arthritis: A Systematic Review and Meta-Analysis. *Mayo Clin Proc.* 2020;95(7):1404-1419.

Polyarticular Juvenile Idiopathic Arthritis (PJIA)

Initial Evaluation

- I. **Tofacitinib (Xeljanz) or upadacitinib (Rinvoq)** may be considered medically necessary when the following criteria below are met:
 - A. Member is being managed by, or in consultation with, a rheumatologist; **AND**
 - B. A diagnosis of **Polyarticular Juvenile Idiopathic Arthritis (PJIA)** when the following are met when the following are met:
 1. Treatment with at least one oral, non-biologic, non-specialty disease-modifying antirheumatic drug (DMARD) has been ineffective, contraindicated, or not tolerated. Guidelines direct to use of methotrexate, sulfasalazine, hydroxychloroquine, or leflunomide. Other examples include azathioprine and cyclosporine; **AND**
 - C. Treatment with one or more tumor necrosis factor (TNF) blockers [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], etanercept (Enbrel) etc.] has been ineffective, not tolerated, or contraindicated.

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Member has exhibited improvement or stability of disease symptoms; **AND**
- IV. Agent prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat polyarticular juvenile idiopathic arthritis or another autoimmune condition (e.g., Orencia, Actemra, Remicade, etc.)

Supporting Evidence

- I. The above agent is approved for pediatric patients greater than two years of age with polyarticular juvenile idiopathic arthritis that had an inadequate response or intolerance to TNF inhibitors based on safety and efficacy data from randomized-controlled trials.
- II. Juvenile idiopathic arthritis (JIA) is a grouping of inflammatory disorders that affect children. Polyarticular juvenile idiopathic arthritis (PJIA) is a subset of JIA, which is defined by the presence arthritis in five or more joints during the first six months of illness. Other subsets of JIA include ERA, oligoarthritis (less than five joints affected), systemic juvenile idiopathic arthritis (SJIA; fever, rash, hepatic/splenic/lymphatic involvement), and psoriatic arthritis (psoriasis and dactylitis). While these are distinct disease states, their pathogenesis and presentation are similar so there is significant overlap in effective treatments.

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- III. The 2019 ACR JIA guidelines for non-systemic polyarthritis (PJIA) strongly recommend initial therapy with a DMARD for all patients with JIA and active polyarthritis; methotrexate has the strongest evidence, but sulfasalazine and leflunomide can also be used. Adjunctive therapy with NSAIDs and oral or intra-articular glucocorticoids is common. Regardless of disease activity, initial therapy with a DMARD is recommended over a biologic, though there may be certain situations where a biologic as initial therapy is preferred (i.e., high-risk joints such as cervical spine, wrist, or hip involved). ACR notes that while initial treatment with biologics was studied in the TREAT-JIA and ACUTE-JIA studies, results were not deemed conclusive enough to make recommendations for biologics as initial therapy at this time. For patients with continued moderate to high disease activity, the guidelines recommend adding a TNF inhibitor, abatacept, or tocilizumab as second-line. The ACR guidelines make a conditional recommendation for switching to non-TNF inhibitor biologics (tocilizumab and abatacept) in patients receiving a TNF inhibitor with continued moderate or high disease activity. It is noted that a second TNF inhibitor may be appropriate for patients who had a good initial response to the first TNF inhibitor but had secondary failure due to suspected drug antibodies developing, and that this conditional recommendation stems from data in adult rheumatoid arthritis patients. Juvenile psoriatic arthritis follows the same treatment paradigm.
- IV. A phase 3 double-blind, randomized, placebo-controlled withdrawal study (PROPEL) evaluated the efficacy and safety of tofacitinib (Xeljanz) in patients aged 2-17 years old with active PJIA and who had inadequate response to at least one DMARD or biologic DMARD. The primary endpoint evaluated the occurrence of disease flare at week 44 and was found to be statistically significantly lower in tofacitinib (Xeljanz) group vs the placebo group (29.2 % vs 59.2%, p-value=0.0031). The secondary endpoint found improvements from baseline in questionnaires JIA ACR 30/50/70 and Childhood Health Assessment Questionnaire Disability Index (CHAQ-DI) in tofacitinib vs placebo. Some limitations to the study include potential bias in the open label arm of the study, and the study is unpublished with limited information such as the population of patients currently on DMARD or oral glucocorticoid.
- V. Upadacitinib (Rinvoq) was approved in PJIA based on pharmacokinetic data supporting safe plasma exposure in pediatric participants at the predicted dosages thought to be comparable to those observed in adults with RA and PsA. An open-label, Phase I, part 3 clinical trial demonstrated safety and efficacy in 83 patients ages two to 17. Participants not controlled on a biologic DMARD received weight-base dosing upadacitinib (Rinvoq) up to 156 weeks. Upadacitinib (Rinvoq) was well tolerated and led to improvements in disease activity and physical function based on the JIA ACR 30, 50, and 70 responses and the Juvenile Arthritis Disease Activity scores at week 12. The efficacy was generally consistent with responses in patients with rheumatoid arthritis.
- VI. Dosing for PJIA is based on body weight. Patients with body weight greater than ≥ 40 kg on the oral solution may be switched to Xeljanz 5 mg tablets. Similarly, those with body weight greater than ≥ 30 kg on the oral solution of Rinvoq may be changed to XR 15mg tablets.

References

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Psoriatic Arthritis

Initial Evaluation

- I. **Tofacitinib (Xeljanz/Xeljanz XR) or upadacitinib (Rinvoq)** may be considered medically necessary when the following criteria below are met:
 - A. Member is being managed by, or in consultation with, a rheumatologist or dermatologist; **AND**
 - B. A diagnosis of active **psoriatic arthritis** when the following are met:
 1. Treatment with non-biologic, non-specialty oral small molecules (OSMs) such as methotrexate, leflunomide, sulfasalazine, or cyclosporine has been ineffective, contraindicated, or not tolerated; **OR**
 2. Presence of active, severe disease as indicated by provider assessment and the presence of at least one of the following:
 - i. Erosive disease
 - ii. Elevated CRP or ESR
 - iii. Long-term damage interfering with function (e.g., joint deformities, vision loss)
 - iv. Major impairment of quality of life due to high disease activity at many sites (including dactylitis, enthesitis) or functionally limiting arthritis at a few sites; **AND**
 - C. Treatment with one or more tumor necrosis factor (TNF) blockers [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], etanercept (Enbrel) etc.] has been ineffective, not tolerated, or contraindicated.

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Member has exhibited improvement or stability of disease symptoms; **AND**
- IV. Agent prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat psoriatic arthritis or another auto-immune condition (e.g., Otezla/Otezla XR, Olumiant, etc.)

Supporting Evidence

- I. Tofacitinib (Xeljanz/Xeljanz XR) and upadacitinib (Rinvoq) are approved for adult patients with psoriatic arthritis (PsA) that had an inadequate response or intolerance to tumor necrosis factor

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- (TNF) inhibitors based on safety and efficacy data from randomized-controlled trials. In April 2024, upadacitinib (Rinvoq) received an age expansion in pediatric patients two years of age and older based on pharmacokinetic data supporting safety and efficacy.
- II. The 2018 ACR guidelines for psoriatic arthritis make a conditional recommendation for starting a TNF inhibitor over an OSM as a first-line option for patients who are treatment-naïve with active psoriatic arthritis. This recommendation is based on low- to very-low quality of evidence. Many of the studies in which greater benefit was seen in terms of disease severity or radiographic progression compared methotrexate to TNF inhibitors, however, most patients included in these groups were not truly treatment naïve to OSM medications. Guidelines note that OSM can be used first-line in naïve patients who do not have severe PsA, severe PsO, prefers oral therapy, or has contraindications to TNF inhibitors. In patients who continue to have active disease despite OSM treatment, it is recommended to switch to a TNF inhibitor rather than trying a different OSM.
 - III. According to the 2019 ACR guidelines for juvenile idiopathic arthritis (JIA), which have been described in the PJIA section, treatment of pediatric PsA is similar to adult PsA: oral DMARD as first line, TNF inhibitors or other biologics as second line. Regardless of level of disease activity, initial therapy with a DMARD is recommended over a biologic. However, initial therapy with a biologic may be preferred for patients with risk factors for/involvement of high-risk joints (cervical spine, wrist, hip), high disease activity, and/or those judged by their physician to be at risk of disabling joint disease.
 - IV. A systematic review of RCTs published in 2015 examined differences in terms of ACR20 response with biologic versus synthetic DMARDs. A statistically significant benefit was not demonstrated with methotrexate, cyclosporine, or sulfasalazine. Leflunomide did demonstrate a statistically significant benefit, though the magnitude of benefit was lower than all of the biologic DMARDs analyzed. There are many limitations to this review, such as a large proportion of trials/data that only included a small number of patients (less than 100). A recent study compared the TNF inhibitor etanercept to methotrexate monotherapy in patients naïve to both biologics and methotrexate. Patients treated with etanercept were statistically more likely to achieve ACR20 response at week 24 compared to the methotrexate monotherapy group (difference 9.2%, 95% CI 1.0 to 17.3, $p = 0.029$).
 - V. The 2018 ACR guidelines for psoriatic arthritis also conditionally recommend for use of a TNF inhibitor biologics over IL-17 inhibitors (ixekizumab, secukinumab) or IL-12/23 inhibitors (ustekinumab). As of January 2022, guidelines have not been updated to place upadacitinib in the PsA treatment algorithm.

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1. Tofacitinib (Xeljanz/Xeljanz XR) [Prescribing Information]. New York, NY; Pfizer Inc., Updated January 2022.
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Ankylosing Spondylitis

Initial Evaluation

- I. **Tofacitinib (Xeljanz) or upadacitinib (Rinvoq)** may be considered medically necessary when the following criteria below are met:
 - A. Member is being managed by, or in consultation with, a rheumatologist; **AND**
 - B. A diagnosis of **Ankylosing Spondylitis (Axial Spondyloarthritis)** when the following are met:
 1. High disease activity (e.g., bothersome chronic neck, back, or hip pain, peripheral joint pain, morning stiffness, fatigue, objective signs of inflammation, functional impairment, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of ≥ 4 , Ankylosing Spondylitis Disease Activity Score (ASDAS) ≥ 2.1); **AND**
 2. Treatment with at least two different Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) (e.g., indomethacin, meloxicam, celecoxib, naproxen, nabumetone, etc.) over four weeks has been ineffective, contraindicated, or not tolerated; **AND**
 - C. Treatment with one or more tumor necrosis factor (TNF) blockers [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], etanercept (Enbrel) etc.] has been ineffective, not tolerated, or contraindicated.

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Member has exhibited improvement or stability of disease symptoms; **AND**
- IV. Agent prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat ankylosing spondylitis or another auto-immune condition (e.g., Otezla/Otezla XR, Olumiant, infliximab, etc.)

Supporting Evidence

- I. Tofacitinib (Xeljanz) and upadacitinib (Rinvoq) are approved for adult patients with active ankylosing spondylitis (AS or ax-SpA) that had an inadequate response or intolerance to TNF inhibitors based on safety and efficacy data from randomized-controlled trials.
- II. Axial spondyloarthritis (SpA or axSpA) is an umbrella term which is comprised of ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA). Ankylosing spondylitis (AS) is an older term and is used interchangeably with the term axial spondyloarthritis (SpA or axSpA). AS or axSpA or SpA or r-axSpA and nr-axSpA represent two stages of the same disease: the nr-axSpA represents an earlier stage without definite radiographic sacroiliitis. In contrast, definitive radiographic changes on X-ray are present with AS. However, not all nr-axSpA patients progress to AS. Additionally, it has been shown that axSpA and nr-axSpA are largely similar with regard to burden of disease, including the presence of comorbidities, treatment received and response. Since typical signs and symptoms of SpA do not depend on the degree of SI joint damage, patients' symptoms present similarly. On average, loss of function and work impairment in nr-axSpA and AS are comparable. Both manifestations deserve the same level of

treatment and care. Clinical guideline recommendations for both axSpA and nr-axSpA follow the same recommendations with variable quality of evidence.

- III. SpA is a relapsing remitting disease. When the disease is active it is characterized by chronic low back pain, swelling, and inflammation with a usual onset before 45 years of age. The disease is also commonly associated with insidious onset, fatigue, morning stiffness, improvement of symptoms with exercise, HLA-B27 positivity, elevated markers of inflammation such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Peripheral manifestations are also possible and include peripheral arthritis, enthesitis, and dactylitis. Peripheral arthritis commonly presents as arthritis of the knees, ankles etc., enthesitis which is inflammation of entheses, (site of insertion of ligaments, tendons, joint capsule, or fascia to bone) commonly manifests as swelling at the heels, at the insertion of the Achilles tendon, or at the insertion of the plantar fascia ligament into the calcaneus, and dactylitis (sausage digits) manifests as swollen digits. Lastly, extramusculoskeletal manifestations (EMMs) are possible, which include uveitis/iritis, skin psoriasis, and inflammatory bowel disease (IBD). In patients SpA and comorbid EMMs, comorbidities often guide therapeutic choices.
- IV. Diagnosis of SpA is challenging which requires weighing of multiple risk factors and is based on clinical presentation in combination with laboratory and imaging tests and exclusion of other more likely diagnoses. Importantly, diagnosis is not made based on Assessment of SpondyloArthritis international society (ASAS) axSpA classification criteria, which is only used for research purposes. Although inflammatory back pain alone is not sufficient to diagnose SpA, its presence is an important initial step in preselection of patients with a high probability of SpA. Other typical features of SpA include good initial response to NSAIDs, peripheral manifestations, EMMs, positive family history, elevated lab markers such CRP and ESR, and HLA-B27 positivity. Imaging (plain radiography or X-ray) can detect sacroiliitis of the axial skeleton in patients with radiographic changes (AS). Patients that are not positive for sacroiliitis by plain imaging or X-rays can undergo MRI to detect inflammatory changes of the joints. Patients without abnormalities on imaging (X-ray or MRI) but with other SpA typical features (symptoms, lab markers, etc.) can be diagnosed with nr-axSpA.
- V. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score (ASDAS) are scoring instruments that assess disease activity when monitoring patients with SpA. ASDAS incorporates patient perspectives of their disease activity and includes CRP as an objective measure of inflammation while BASDAI reflects only the patient perspective. Both instruments incorporate questions that assess the level of fatigue, pain, swelling, discomfort, and morning stiffness. While the 2022 ASAS-EULAR clinical guidelines endorse the use of these instruments in clinical practice to determine when escalation in therapy may be needed and to determine response to treatment, the use of these instruments to determine treatment intensification or baseline disease activity is not strongly recommended in the 2019 ACR/SAA/SPARTAN guidelines. The 2019 ACR/SAA/SPARTAN guidelines conditionally recommend regular-interval use and monitoring of a validated AS disease activity measure and conditionally recommend regular-interval use and monitoring of the CRP concentrations or ESR over usual care. The 2019 ACR/SAA/SPARTAN guidelines further note that no studies addressed the effect of routine monitoring of a disease activity measure, such as the BASDAI or the ASDAS, or acute-phase reactants on outcomes in patients with AS. In clinical settings, the use of BASDAI and ASDAS instruments is not uniformly adopted and other factors other than disease activity often play a role when making treatment decisions. Medical necessity for treatment escalation to a biologic or Janus Kinase (JAK) inhibitor requires that patients have high disease activity which may be defined by BASDAI or ASDAS scores if available or could be determined by a positive rheumatologists' opinion to escalate treatment based on prior failure of conventional

- therapies (e.g., NSAIDs) and a clinical exam which evaluates presence of ongoing bothersome symptoms, as well as laboratory exams that support ongoing inflammation.
- VI. The 2019 ACR/SAA/SPARTAN and the 2022 ASAS-EULAR guidelines on the treatment of ankylosing spondylitis strongly recommend the use of NSAIDs as first-line treatment (with 70-80% patients responding). No particular NSAID has been determined to be superior in efficacy or safety and guidelines don't recommend a preferred choice. Guidelines recommend that lack of response (or intolerance) to at least two different NSAIDs at maximal doses over one month, or incomplete responses to at least two different NSAIDs over 2 months, would be adequate trials with which to judge NSAID responsiveness prior to escalating to treatment with Tumor Necrosis Factor (TNF) inhibitors.
 - VII. For those patients with inadequate response despite continuous NSAID treatment, the 2019 ACR/SAA/SPARTAN panel recommends the use of TNF inhibitors as the preferred next choice due to experience and familiarity with their long-term safety and toxicity. Guidelines do not recommend any particular TNF inhibitor as the preferred choice. For those patients with continued active disease, the panel conditionally recommends a trial of a different TNF inhibitor over treatment with a non-TNF inhibitor in patients with secondary nonresponse to TNF inhibitor (those that initially responded and subsequently lost response over time). In patients that never responded to a first trial of a TNF inhibitor (primary nonresponse), trial of a different TNF inhibitor is not recommended and use of subsequent biologics or JAK inhibitors is preferred. Patients presenting with peripheral arthritis symptoms have additional treatment options before escalating to a biologic, which include sulfasalazine and local glucocorticoid (GC) injections. GC injections may also be used in patients with isolated sacroiliitis.
 - VIII. In patients with intolerance, contraindications, or loss of efficacy with TNF inhibitors, the 2019 ACR/SAA/SPARTAN guidelines recommend IL-17A inhibitors next, followed by JAK inhibitors. Precautions for cardiovascular risk, malignancy, and thromboembolic events should be considered in patients starting JAK inhibitors. It is unclear whether the increased risk of cardiovascular events and malignancies is specific to a diagnosis of Rheumatoid Arthritis (RA), reflective of a JAK inhibitor class effect, or specific to tofacitinib (Xeljanz). Until more data becomes available, the 2022 ASAS-EULAR guidelines advise against starting JAK inhibitors in specific populations: patients above 50 years of age with one or more cardiovascular risk factor and patients older than 65 years of age.
 - IX. According to the 2022 ASAS-EULAR and 2019 ACR/SAA/SPARTAN guidelines, treatment decisions may differ for patients presenting with EMMs. For example, for those with SpA and comorbid uveitis/iritis, adalimumab, infliximab, golimumab, and certolizumab pegol may be preferred over etanercept as this TNF inhibitor showed contradictory results. Secukinumab was shown to be unsuccessful in patients with non-infectious uveitis while rates of uveitis flares with ixekizumab have not been well-defined. For patients with comorbid inflammatory bowel disease (IBD), TNF inhibitors are preferred (except etanercept which is not effective in IBD). Secukinumab has been associated with the new onset, or exacerbation, of Crohn's disease. Increased risks of IBD exacerbation appear to also occur with ixekizumab. For psoriasis and SpA, guidelines suggest that IL-17 inhibitors may be preferred, however, no comparative data is available on psoriasis patients with axSpA. For the treatment of psoriasis and SpA, a product that is FDA approved for both indications is preferred.
 - X. The 2019 ACR/SAA/SPARTAN guidelines conditionally recommend against the addition of sulfasalazine or methotrexate to biologic drugs and do not recommend these treatments for those with predominantly axial disease symptoms. This is based off controlled trials demonstrating minimal to no benefit with agents such as sulfasalazine, methotrexate, and leflunomide. Some benefit has been seen in patients with peripheral arthritis, and thus these

agents may be considered for patients with ankylosing spondylitis with predominantly peripheral arthritis symptoms. Similar recommendations are made by the 2022 ASAS/EULAR guidelines.

- XI. There is no specific treatment algorithm after primary non-response to biologic (TNF inhibitor or IL-17 inhibitor) or JAK inhibitor therapy. In absence of data showing superiority in the treatment sequence, switching to another biologic DMARD (TNF inhibitor or IL-17 inhibitor) or a JAK inhibitor may be considered.

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Non-radiographic Axial Spondyloarthritis

Initial Evaluation

- I. **Upadacitinib (Rinvoq)** may be considered medically necessary when the following criteria below are met:
 - A. Member is being managed by, or in consultation with, a rheumatologist; **AND**
 - B. A diagnosis of **Non-radiographic Axial Spondyloarthritis** when the following are met:
 1. High disease activity (e.g., bothersome chronic neck, back, or hip pain, peripheral joint pain, morning stiffness, fatigue, objective signs or inflammation, functional impairment, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score ≥ 4 , Ankylosing Spondylitis Disease Activity Score (ASDAS) score ≥ 2.1 ; **AND**
 2. Treatment with at least two different Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) (e.g., indomethacin, meloxicam, celecoxib, naproxen, nabumetone, etc.) over four weeks has been ineffective, contraindicated, or not tolerated; **AND**
 - C. Treatment with one or more tumor necrosis factor (TNF) blockers [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], etanercept (Enbrel), certolizumab (Cimzia), etc.] has been ineffective, not tolerated, or contraindicated

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Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Member has exhibited improvement or stability of disease symptoms; **AND**
- IV. Agent prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat non-radiographic axial spondyloarthritis or another autoimmune condition (e.g., Otezla/Otezla XR, Olumiant, Infliximab, etc.)

Supporting Evidence

- I. Upadacitinib (Rinvoq) is the only JAK inhibitor that is FDA-approved for adult patients with active non-radiographic axial spondyloarthritis (nr-axSpA) that had an inadequate response or intolerance to TNF inhibitors based on safety and efficacy data from randomized-controlled trials.
- II. Currently, upadacitinib, certolizumab pegol, ixekizumab, secukinumab, and bimekizumab are the only FDA approved agent for adults with nr-axSpA. All FDA approved drugs were studied in Phase 3 studies which demonstrated statistically significant improvements in ASAS 40 response and other outcomes. Other TNF inhibitors are approved in Europe for this indication, have demonstrated efficacy in RCTs, and are utilized frequently in clinical practice. A study of 192 patients taking adalimumab demonstrated significant improvement compared to placebo in ASAS40 response by week 12 in patients with non-radiographic disease (36% vs 15%, $p < 0.001$). Likewise, etanercept and golimumab have also been approved by the European Medicines Agency, and the 2022 ASAS/EULAR guidelines note that efficacy in regard to musculoskeletal signs and symptoms appears comparable based off indirect comparison.
- III. Axial spondyloarthritis (SpA or axSpA) is an umbrella term which is comprised of ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA). Ankylosing spondylitis (AS) is an older term and is used interchangeably with the term axial spondyloarthritis (SpA or axSpA). AS or axSpA or SpA or r-axSpA and nr-axSpA represent two stages of the same disease: the nr-axSpA represents an earlier stage without definite radiographic sacroiliitis. In contrast, definitive radiographic changes on X-ray are present with AS. However, not all nr-axSpA patients progress to AS. Additionally, it has been shown that axSpA and nr-axSpA are largely similar with regard to burden of disease, including the presence of comorbidities, treatment received and response. Since typical signs and symptoms of SpA do not depend on the degree of SI joint damage, patients' symptoms present similarly. On average, loss of function and work impairment in nr-axSpA and AS are comparable. Both manifestations deserve the same level of treatment and care. Clinical guideline recommendations for both axSpA and nr-axSpA follow the same recommendations with variable quality of evidence.
- IV. SpA is a relapsing remitting disease. When the disease is active it is characterized by chronic low back pain, swelling, and inflammation with a usual onset before 45 years of age. The disease is also commonly associated with insidious onset, fatigue, morning stiffness, improvement of symptoms with exercise, HLA-B27 positivity, elevated markers of inflammation such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Peripheral manifestations are also possible and include peripheral arthritis, enthesitis, and dactylitis. Peripheral arthritis commonly presents as arthritis of the knees, ankles etc., enthesitis which is inflammation of

entheses, (site of insertion of ligaments, tendons, joint capsule, or fascia to bone) commonly manifests as swelling at the heels, at the insertion of the Achilles tendon, or at the insertion of the plantar fascia ligament into the calcaneus, and dactylitis (sausage digits) manifests as swollen digits. Lastly, extramusculoskeletal manifestations (EMMs) are possible, which include uveitis/iritis, skin psoriasis, and inflammatory bowel disease (IBD). In patients SpA and comorbid EMMs, comorbidities often guide therapeutic choices.

- V. Per 2019 ACR/SAA/SPARTAN non-radiographic axial spondyloarthritis treatment guidelines, the panel strongly recommends treatment with TNF inhibitors over no treatment with TNF inhibitors. Moreover, the panel conditionally recommends treatment with TNF inhibitors over treatment with secukinumab or ixekizumab and conditionally recommends treatment with secukinumab or ixekizumab over tofacitinib. In patients with primary nonresponse to the first TNF inhibitor, the panel conditionally recommends switching to secukinumab or ixekizumab over switching to a different TNF inhibitor. A systematic review by Corbett et al published in 2016 demonstrated significant improvement in disease state measures such as the ASAS20 and BASDAI50 in patients with non-radiographic axial spondyloarthritis taking TNF inhibitors such as adalimumab, certolizumab pegol, etanercept, and infliximab.
- VI. Diagnosis of SpA is challenging which requires weighing of multiple risk factors and is based on clinical presentation in combination with laboratory and imaging tests and exclusion of other more likely diagnoses. Importantly, diagnosis is not made based on Assessment of SpondyloArthritis international society (ASAS) axSpA classification criteria, which is only used for research purposes. Although inflammatory back pain alone is not sufficient to diagnose SpA, its presence is an important initial step in preselection of patients with a high probability of SpA. Other typical features of SpA include good initial response to NSAIDs, peripheral manifestations, EMMs, positive family history, elevated lab markers such CRP and ESR, and HLA-B27 positivity. Imaging (plain radiography or X-ray) can detect sacroiliitis of the axial skeleton in patients with radiographic changes (AS). Patients that are not positive for sacroiliitis by plain imaging or X-rays can undergo MRI to detect inflammatory changes of the joints. Patients without abnormalities on imaging (X-ray or MRI) but with other SpA typical features (symptoms, lab markers, etc.) can be diagnosed with nr-axSpA.
- VII. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score (ASDAS) are scoring instruments that assess disease activity when monitoring patients with SpA. ASDAS incorporates patient perspectives of their disease activity and includes CRP as an objective measure of inflammation while BASDAI reflects only the patient perspective. Both instruments incorporate questions that assess the level of fatigue, pain, swelling, discomfort, and morning stiffness. While the 2022 ASAS-EULAR clinical guidelines endorse the use of these instruments in clinical practice to determine when escalation in therapy may be needed and to determine response to treatment, the use of these instruments to determine treatment intensification or baseline disease activity is not strongly recommended in the 2019 ACR/SAA/SPARTAN guidelines. The 2019 ACR/SAA/SPARTAN guidelines conditionally recommend regular-interval use and monitoring of a validated AS disease activity measure and conditionally recommend regular-interval use and monitoring of the CRP concentrations or ESR over usual care. The 2019 ACR/SAA/SPARTAN guidelines further note that no studies addressed the effect of routine monitoring of a disease activity measure, such as the BASDAI or the ASDAS, or acute-phase reactants on outcomes in patients with AS. In clinical settings, the use of BASDAI and ASDAS instruments is not uniformly adopted and other factors other than disease activity often play a role when making treatment decisions. Medical necessity for treatment escalation to a biologic or Janus Kinase (JAK) inhibitor requires that patients have high disease activity which may be defined by BASDAI or ASDAS scores if available or could be determined by a

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positive rheumatologists' opinion to escalate treatment based on prior failure of conventional therapies (e.g., NSAIDs) and a clinical exam which evaluates presence of ongoing bothersome symptoms, as well as laboratory exams that support ongoing inflammation.

- VIII. The 2019 ACR/SAA/SPARTAN and the 2022 ASAS-EULAR guidelines on the treatment of ankylosing spondylitis strongly recommend the use of NSAIDs as first-line treatment (with 70-80% patients responding). No particular NSAID has been determined to be superior in efficacy or safety and guidelines don't recommend a preferred choice. Guidelines recommend that lack of response (or intolerance) to at least two different NSAIDs at maximal doses over one month, or incomplete responses to at least two different NSAIDs over 2 months, would be adequate trials with which to judge NSAID responsiveness prior to escalating to treatment with Tumor Necrosis Factor (TNF) inhibitors.
- IX. For those patients with inadequate response despite continuous NSAID treatment, the 2019 ACR/SAA/SPARTAN panel recommends the use of TNF inhibitors as the preferred next choice due to experience and familiarity with their long-term safety and toxicity. Guidelines do not recommend any particular TNF inhibitor as the preferred choice. For those patients with continued active disease, the panel conditionally recommends a trial of a different TNF inhibitor over treatment with a non-TNF inhibitor in patients with secondary nonresponse to TNF inhibitor (those that initially responded and subsequently lost response over time). In patients that never responded to a first trial of a TNF inhibitor (primary nonresponse), trial of a different TNF inhibitor is not recommended and use of subsequent biologics or JAK inhibitors is preferred. Patients presenting with peripheral arthritis symptoms have additional treatment options before escalating to a biologic, which include sulfasalazine and local glucocorticoid (GC) injections.
- X. In patients with intolerance, contraindications, or loss of efficacy with TNF inhibitors, the 2019 ACR/SAA/SPARTAN guidelines recommend IL-17A inhibitors next, followed by JAK inhibitors. Precautions for cardiovascular risk, malignancy, and thromboembolic events should be considered in patients starting JAK inhibitors. It is unclear whether the increased risk of cardiovascular events and malignancies is specific to a diagnosis of Rheumatoid Arthritis (RA), reflective of a JAK inhibitor class effect, or specific to tofacitinib (Xeljanz). Until more data becomes available, the 2022 ASAS-EULAR guidelines advise against starting JAK inhibitors in specific populations: patients above 50 years of age with one or more cardiovascular risk factor and patients older than 65 years of age.
- XI. According to the 2022 ASAS-EULAR and 2019 ACR/SAA/SPARTAN guidelines, treatment decisions may differ for patients presenting with EMMs. For example, for those with SpA and comorbid uveitis/iritis, adalimumab, infliximab, golimumab, and certolizumab pegol may be preferred over etanercept as this TNF inhibitor showed contradictory results. Secukinumab was shown to be unsuccessful in patients with non-infectious uveitis while rates of uveitis flares with ixekizumab have not been well-defined. For patients with comorbid inflammatory bowel disease (IBD), TNF inhibitors are preferred (except etanercept which is not effective in IBD). Secukinumab has been associated with the new onset, or exacerbation, of Crohn's disease. Increased risks of IBD exacerbation appear to also occur with ixekizumab. For psoriasis and SpA, guidelines suggest that IL-17 inhibitors may be preferred, however, no comparative data is available on psoriasis patients with axSpA. For the treatment of psoriasis and SpA, a product that is FDA approved for both indications is preferred.
- XII. The 2019 ACR/SAA/SPARTAN guidelines conditionally recommend against the addition of sulfasalazine or methotrexate to biologic drugs and do not recommend these treatments for those with predominantly axial disease symptoms. This is based off controlled trials demonstrating minimal to no benefit with agents such as sulfasalazine, methotrexate, and

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leflunomide. Some benefit has been seen in patients with peripheral arthritis, and thus these agents may be considered for patients with ankylosing spondylitis with predominantly peripheral arthritis symptoms. Similar recommendations are made by the 2022 ASAS/EULAR guidelines.

- XIII. There is no specific treatment algorithm after primary non-response to biologic (TNF inhibitor or IL-17 inhibitor) or JAK inhibitor therapy. In absence of data showing superiority in the treatment sequence, switching to another biologic DMARD (TNF inhibitor or IL-17 inhibitor) or a JAK inhibitor may be considered.

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Plaque Psoriasis

Initial Evaluation

- I. **Deucravacitinib (Sotyktu)** may be considered medically necessary when the following criteria are met:
 - A. Medication is prescribed by, or in consultation with a dermatologist; **AND**
 - B. Not used in combination with other biologics or other non-biologic specialty medications [e.g., apremilast [Otezla/Otezla XR], adalimumab (Humira), risankizumab (Skyrizi)] used to treat autoimmune conditions; **AND**
 - C. A diagnosis of **moderate-to severe-plaque psoriasis** when the following are met:
 1. Chronic disease (greater than 6 months); **AND**
 2. At least 10% body surface area is involved or involves areas of the face, ears, hands, feet or genitalia; **AND**
 3. Treatment with the following has been ineffective or not tolerated, or all are contraindicated;

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- i. Phototherapy (UVB or PUVA); **OR**
 - a. At least one non-biologic, non-specialty DMARD (e.g., methotrexate, cyclosporine, acitretin, etc.); **AND**
 - ii. Treatment with adalimumab [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], etanercept (Enbrel), secukinumab (Cosentyx), ustekinumab [e.g., ustekinumab-aekn (Selarsdi), ustekinumab-kfce (Yesintek), ustekinumab-stba (Steqeyma)], risankizumab (Skyrizi), apremilast (Otezla/Otezla XR), and guselkumab (Tremfya) have been ineffective, contraindicated, or not tolerated.
- II. Deucravacitinib (Sotyktu) is considered investigational when used for all other conditions, including but not limited to:
 - A. Psoriasis in pediatric and adolescent patients
 - B. Psoriatic arthritis
 - C. Lupus erythematosus
 - D. Inflammatory bowel disease

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Member has exhibited improvement or stability of disease symptoms; **AND**
- IV. The medication prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat plaque psoriasis or another auto-immune condition (e.g., Otezla/Otezla XR, Xeljanz, Olumiant, Rinvoq, etc.).

Supporting Evidence

- I. Deucravacitinib (Sotyktu) has been evaluated for the treatment of moderate-to-severe plaque psoriasis in adult patients at a dose of 6 mg daily. Guidelines define moderate psoriasis to be 3-10% of the body surface area (BSA) and severe is defined as greater than or equal to 10% BSA involvement. Psoriasis can be considered severe irrespective of BSA when it occurs in certain locations (e.g., hands, feet, face, genital area). Guidelines provide a Grade A recommendation for use of biologics and apremilast (Otezla/Otezla XR) for the treatment of moderate-to-severe plaque psoriasis. Guidelines do not point to a specific agent or class when initiating treatment with a biologic or other oral specialty therapy. Flares of psoriasis may be transient and may not require systemic therapy; thus, disease duration of six months is required to determine medical necessity for systemic therapy.
- II. Guidelines indicate that the majority of patients are capable of adequately controlling disease solely with topical medications or phototherapy. Phototherapy is recognized as a beneficial therapy for controlled plaque psoriasis and is a cost-effective treatment strategy. Additionally, oral immunomodulatory medications (e.g., methotrexate, cyclosporine, acitretin) are cost-effective therapies with a well-known safety profile for the treatment of plaque psoriasis. For moderate-to-severe disease, where a JAK inhibitor or biologics are warranted, deucravacitinib (Sotyktu) is one of many options. However, it would not be indicated for mild psoriasis given that patients are better managed from a safety perspective on well-established therapies (e.g.,

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topical agents, phototherapy, conventional DMARDS, apremilast [Otezla/Otezla XR]). Although deucravacitinib (Sotyktu) has been evaluated and showed to be superior to apremilast (Otezla/Otezla XR) in clinical trials for patients with moderate to severe psoriasis, regarding the extent of patients able to achieve outcomes such as PASI75 and PGA0/1, results cannot be readily applied to patients with mild psoriasis. Given the largely unknown safety profile of deucravacitinib (Sotyktu) overall, the risk-to-benefit ratio of using deucravacitinib (Sotyktu) in mild disease is unknown. Alternatively, established therapies should continue to be the mainstay of therapy for these patients.

- III. In terms of efficacy, deucravacitinib (Sotyktu) has shown superiority only to apremilast (Otezla/Otezla XR) in clinical trials; however, it joins many other efficacious therapies that have well-established safety profiles (e.g., TNF- α inhibitors, IL-17, IL23 therapies). In clinical trials, 50-60% patients on deucravacitinib (Sotyktu) met PASI75. When indirectly comparing, it is not likely superior to the majority of established biologics for psoriasis. Additionally, within the last few years, there has been great improvement in outcomes patients are able to achieve with newer, targeted therapies for psoriasis. Notably, the potential for patients reaching PASI90 and PASI100 within a year of treatment has greatly increased, leading to a rethinking of primary and secondary endpoints evaluated as the standard. For example, 40-60% of patients treated with IL-17 and IL-23 therapies met PASI100 at one year in recent clinical trials. Given established safety profiles, known efficacy, and cost-effectiveness, trial of preferred psoriasis therapies such as biologics as listed in the criteria, are required for trial and failure or intolerance, unless contraindicated.
- IV. In subgroup analyses in deucravacitinib (Sotyktu) trials patients with a BMI of 35 kg/m² or greater may not as readily respond to deucravacitinib (Sotyktu) compared to patients under 35 kg/m² BMI with otherwise similar characteristics; however, there is no evidence for safety and efficacy for up dosing beyond 6 mg. There is largely unknown safety profile for this new JAK therapy, and the full extent of the safety profile is likely to be realized from real-world data when duration of use is extended and used in larger patient populations. Until data are available to confirm safety and efficacy of more than 6 mg per day, quantity exceptions will not be allowed.

Investigational or Not Medically Necessary Uses

- I. Deucravacitinib (Sotyktu) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Psoriasis in pediatric and adolescent patients
 - B. Psoriatic arthritis
 - C. Lupus erythematosus
 - D. Inflammatory bowel disease

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Crohn's Disease

Initial Evaluation

- I. **Upadacitinib (Rinvoq)** may be considered medically necessary when the following criteria below are met:
 - A. Member is being managed by, or in consultation with, a gastroenterologist; **AND**
 - B. Diagnosis of **moderate to severe Crohn's disease**; **AND**
 - C. Provider attestation or clinical documentation of at least one of the following:
 1. Treatment with systemic corticosteroids (e.g., prednisone, budesonide) has been ineffective, contraindicated, or not tolerated; **OR**
 2. Treatment with an immunomodulator (e.g., methotrexate, azathioprine, 6-mercaptopurine) has been ineffective, contraindicated, or not tolerated; **OR**
 3. Provider attestation or clinical documentation of high-risk disease (e.g., symptoms despite conventional therapy, obstruction, abscess, stricture, phlegmon, fistulas, resection, extensive bowel involvement, early age of onset, growth retardation); **AND**
 - D. Treatment with one or more tumor necrosis factor (TNF) blockers [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], infliximab (Remicade) etc.] has been ineffective, not tolerated, or contraindicated

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Member has exhibited improvement or stability of disease symptoms; **AND**
- IV. Agent prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat Crohn's disease or another auto-immune condition (e.g., Otezla/Otezla XR, Xeljanz, Olumiant, Infliximab, etc.)

Supporting Evidence

- I. Upadacitinib (Rinvoq) is FDA approved for the treatment of moderate to severe Crohn's Disease (CD) based on safety and efficacy data from randomized-controlled trials. Certolizumab pegol (Cimzia), ustekinumab (Stelara), risankizumab (Skyrizi) and upadacitinib (Rinvoq) are FDA-approved in adults only, while adalimumab (Humira) is approved in patients six years of age and older.
- II. Diagnosis of CD is based on a combination of clinical presentation, endoscopic, radiologic, histologic, and pathologic findings that demonstrate inflammation of the luminal GI tract. As such, it is recommended that diagnosis is made by a provider specialized in detecting and treating inflammatory bowel diseases, such as a gastroenterologist.
- III. Therapeutic recommendations for patients with CD are established based upon disease location, disease severity, disease associated complications, and future disease prognosis. The goals of therapy are to induce remission, prevent relapse, and prevent the occurrence of disease complications, such as stricture and fistula.

Moderate to severe CD

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- IV. According to the 2018 American College of Gastroenterology (ACG) guidelines patients with moderate to severe CD are considered to have failed to respond to treatment for mild to moderate disease, or those with more prominent symptoms of fever, significant weight loss, abdominal pain or tenderness, intermittent nausea or vomiting (without obstructive findings), or significant anemia. They have moderate to severely active endoscopic mucosal disease and disease activity corresponding to Crohn's Disease Activity Index (CDAI) score of 220-450.
- V. Symptoms of CD do not correlate well with the presence of active inflammation and therefore should not be the sole guide for therapy. Objective evaluation by endoscopic imaging should be undertaken to avoid errors of under or overtreatment.
- VI. Patients with CD are at risk of developing intestinal complications such as strictures, abscess, fistula, or phlegmon formation. According to the 2018 ACG guidelines features associated with high risk for progressive disease include age at diagnosis, initial extensive bowel involvement, ileal/ileocolonic or proximal gastrointestinal (GI) involvement, perianal/severe rectal disease, and patients presenting with a penetrating or stenosis disease phenotype.
- VII. For patients with moderate to severe disease and those with moderate to high-risk disease, the 2018 ACG guidelines recommend treatment with oral corticosteroids used short term to induce remission (strong recommendation, moderate level of evidence). However, it is noted that one in five patients will become steroid refractory which is thought to be the result of unreliable efficacy in healing of the mucosa associated with steroids (weak recommendation, low level of evidence). Corticosteroids are also implicated in the development of perforating complications (abscess and fistula) and are relatively contraindicated in those patients. The 2021 American Gastroenterological Association (AGA) clinical guidelines make similar recommendations and suggest the use of corticosteroids in adult outpatients with moderate to severe CD over no treatment for induction of remission (conditional recommendation, moderate level of evidence).
- VIII. In patients with moderate to severe CD who remain symptomatic despite current or prior corticosteroid therapy, 2018 ACG guidelines recommend immunomodulators such as azathioprine, 6-mercaptopurine (strong recommendation, moderate level of evidence), and methotrexate (conditional recommendation, low level of evidence) to be effective for maintenance of remission. Due to slow time to clinical response that may not be evident for as long as 12 weeks, these agents are not recommended for short-term induction. The 2021 AGA guidelines make similar suggestions and recommend the use of thiopurines over no treatment for the maintenance of remission (conditional recommendation, low level of evidence).
- IX. ACG guidelines recommend anti-TNF-alpha agents (infliximab [e.g., Remicade, Inflectra], adalimumab [Humira], certolizumab pegol [Cimzia]) in patients resistant to treatment with corticosteroids and refractory to thiopurines or methotrexate (strong recommendation, moderate level of evidence). Additionally, combination therapy of infliximab (e.g., Remicade, Inflectra) with immunomodulators (thiopurines) is more effective than treatment with either immunomodulators alone or infliximab (e.g., Remicade, Inflectra) alone in patients who are naïve to those agents (strong recommendation, high level of evidence). Recommendations are also made regarding the use of vedolizumab (Entyvio), natalizumab (Tysabri), and ustekinumab (Stelara) without preference for one biologic over the other. The AGA guidelines recommend early introduction of biologics with or without immunomodulators rather than delaying their use until after failure of 5-aminosalicylates and/or corticosteroids; however, this recommendation is conditional with low certainty of evidence.
- X. Adalimumab (Humira), ustekinumab (Stelara), certolizumab (Cimzia), infliximab (e.g., Remicade, Inflectra), vedolizumab (Entyvio), natalizumab (Tysabri), risankizumab (Skyrizi), and upadacitinib (Rinvoq) have not been studied in head-to-head trials to compare the efficacy and safety

between these agents. Results from studies of each agent against placebo have shown statistically and clinically significant efficacy outcomes in inducing and maintaining remission during their respective pivotal trials. The net health benefit provided by all biologic agents FDA approved for the treatment of moderate to severe CD in adults is incremental or better when evaluated against placebo.

- XI. The timing of introduction of biologic agents is a matter of debate and more studies are needed to assess stepwise approach versus earlier administration of biologic agents in patients with moderate to severe disease. The 2019 British Society of Gastroenterology guidelines suggest that systemic corticosteroids are still an effective initial therapy for uncomplicated luminal moderate to severe disease, regardless of disease location; however, every effort should be made to limit exposure (strong recommendation, high-quality evidence). In patients with an aggressive disease course, or high risk, poor prognostic factors, early introduction of biologics may be considered (weak recommendation, moderate-quality evidence). High risk features include extensive disease, complex (stricturing or penetrating disease), perianal fistulizing disease, age under 40 years at diagnosis, and the need for steroids to control index flare; however, the predictive power of these features is limited.

High-risk/severe CD

- XII. Patients who are considered to have severe/fulminant disease are those with persistent symptoms despite the introduction of conventional corticosteroids or biologic agents as outpatients, or individuals presenting with high fevers, persistent vomiting, evidence of intestinal obstruction, significant peritoneal signs such as involuntary guarding or rebound tenderness, cachexia, or evidence of an abscess. They have endoscopic or radiographic evidence of severe mucosal disease and disease activity corresponding to CDAI score of >450.
- XIII. Collective evidence suggests that initial treatment with biologics may be considered for patients with the following disease features: severe CD (CDAI >450, evidence of intestinal obstruction, abscess, stricture, or phlegmon, and endoscopic or radiographic evidence of severe mucosal disease such as deep ulcerations), perianal fistulizing disease, and pre- and post-operative CD. Additional consideration may be given to patients presenting with other poor prognostic factors (e.g., extensive bowel involvement, early age of onset) and should be evaluated on case-by-case basis.

References

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Ulcerative Colitis

Initial Evaluation

- I. **Tofacitinib (Xeljanz/Xeljanz XR) or upadacitinib (Rinvoq)** may be considered medically necessary when the following criteria below are met:
 - A. Member is being managed by, or in consultation with, a gastroenterologist; **AND**
 - B. Diagnosis of **moderate to severe ulcerative colitis**; **AND**
 - C. Provider attestation or clinical documentation of at least one of the following:
 1. Treatment with systemic corticosteroids (e.g., prednisone, budesonide) has been ineffective, contraindicated, or not tolerated; **OR**
 2. Treatment with an immunomodulator (e.g., azathioprine, 6-mercaptopurine) has been ineffective, contraindicated, or not tolerated; **AND**
 - E. Treatment with one or more tumor necrosis factor (TNF) blockers [e.g., adalimumab-bwwd (Hadlima), adalimumab-adaz (Adalimumab-ADAZ)], infliximab (Remicade) etc.] has been ineffective, not tolerated, or contraindicated.

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Member has exhibited improvement or stability of disease symptoms; **AND**
- IV. Agent prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat ulcerative colitis or another auto-immune condition (e.g., Remicade, Entyvio, Cimzia, etc.)

Supporting Evidence

- I. Tofacitinib (Xeljanz/Xeljanz XR) and upadacitinib (Rinvoq) are FDA approved in the treatment of moderate to severe ulcerative colitis (UC) in adult patients over eighteen years of age that had an inadequate response or intolerance to one or more TNF inhibitors based on safety and efficacy data from randomized-controlled trials. As of May 2021, only adalimumab (Humira) has been FDA approved in moderate to severe ulcerative colitis in pediatric patients aged 5 years and older.
- II. Adalimumab (Humira), tofacitinib (Xeljanz), ustekinumab (Stelara), golimumab (Simponi), ozanimod (Zeposia), upadacitinib (Rinvoq), mirikizumab (Omvo), etrasimod (Velsipity), infliximab-dyyb (Zymfentra), and risankizumab (Skyrizi), have not been evaluated in head-to-head trials to compare the efficacy and safety between these agents. Results from studies of each agent against placebo have shown statistically and clinically significant efficacy outcomes in inducing and maintaining remission during their respective pivotal trials. The net health benefit provided by adalimumab (Humira), tofacitinib (Xeljanz), ustekinumab (Stelara), golimumab

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(Simponi), ozanimod (Zeposia), upadacitinib (Rinvoq), mirikizumab (Omnivoh), etrasimod (Velsipity), infliximab-dyyb (Zymfentra), and risankizumab (Skyrizi) is incremental or better when evaluated against placebo. There is moderate certainty that ozanimod (Zeposia) provides promising but inconclusive net health benefit compared to placebo in patients with moderate to severe UC due to evidence being available from only one phase 3 trial and less established safety data compared to other UC treatment options.

- III. The 2019 American College of Gastroenterology (ACG) clinical guideline on the management of ulcerative colitis in adults recommend oral systemic corticosteroids for induction of remission in moderate to severe disease (strong recommendation, moderate quality of evidence). TNF inhibitors (adalimumab, golimumab, and infliximab), vedolizumab (Entyvio), and tofacitinib (Xeljanz) are also recommended for induction of remission (strong recommendation, moderate quality of evidence). For maintenance of remission, thiopurines are recommended if remission was achieved after corticosteroid induction (conditional recommendation, low quality of evidence). The guidelines note a systematic review of 1,632 patients with ulcerative colitis demonstrated that azathioprine and mercaptopurine had a 76% mean efficacy in maintaining remission. If remission was achieved with anti-TNF therapy, vedolizumab (Entyvio), or tofacitinib (Xeljanz), clinical guidelines support continuing with the same agent to maintain remission (strong recommendation, moderate quality of evidence). The 2020 American Gastroenterology Association (AGA) guidelines make similar recommendations. Additionally, AGA recommends early use of biologic agents, rather than gradual step up after failure of 5-ASA in moderate to severe disease at high risk for colectomy. However, the overall quality of evidence supporting this recommendation was rated as very low. Guidelines also note that for patients with less severe disease, 5-ASA therapy may still be a reasonable choice of therapy to start with. For maintenance of remission, AGA makes no recommendation in favor of, or against, using biologic monotherapy, rather than thiopurine monotherapy due to absence of evidence. As of May 2022, the guidelines have not been updated to include upadacitinib (Rinvoq).
- IV. Patients who are primary non-responders to an anti-TNF therapy should be evaluated and considered for alternative mechanisms of disease control (e.g., in a different class of therapy) rather than cycling to another drug within the anti-TNF class. In patients with moderate to severe active ulcerative colitis who had an initial response but subsequently lost efficacy to one anti-TNF therapy, clinical guidelines recommend alternative anti-TNF therapy (but not the biosimilar to the original brand) compared with no treatment for induction of remission.
- V. The 2018 European Crohn's and Colitis Organization and European Society of Pediatric Gastroenterology, Hepatology, and Nutrition clinical guidelines recommend treatment with oral systemic corticosteroids if patients are in the higher end of the moderate disease range and treatment with thiopurines for maintaining remission in children who are corticosteroid-dependent or relapsing frequently despite 5-ASA treatment, and 5-ASA intolerant patients. The guidelines recommend infliximab (e.g., Remicade, Inflectra) in chronically active or steroid-dependent ulcerative colitis, uncontrolled by 5-ASA and thiopurines, for both induction and maintenance of remission. Adalimumab (Humira) or golimumab (Simponi) could be considered in those who initially respond but then lose response or intolerant to infliximab (e.g., Remicade, Inflectra), based on serum levels and antibodies. Vedolizumab (Entyvio) should be considered in chronically active or steroid-dependent patients as second-line biologic therapy after anti-TNF failure.

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Atopic Dermatitis

Initial Evaluation

- I. **Upadacitinib (Rinvoq)** may be considered medically necessary when the following criteria are met:
 - A. Medication is prescribed by, or in consultation with, a dermatologist or an allergist; **AND**
 - B. A diagnosis of **moderate to severe atopic dermatitis** when the following are met:
 1. Body surface area (BSA) involvement of at least 10%; **OR**
 - i. Involves areas of the face, ears, hands, feet, or genitalia; **AND**
 2. Treatment with at least two of the following groups has been ineffective or not tolerated, or all are contraindicated:
 - i. Group 1: topical corticosteroids of at least medium/moderate potency (e.g., clobetasol, betamethasone, halobetasol)
 - ii. Group 2: topical calcineurin inhibitors (e.g., tacrolimus ointment, pimecrolimus cream)
 - iii. Group 3: topical PDE-4 inhibitor (crisaborole [Eucrisa]); **AND**
 3. Documentation that a trial of systemic immunosuppressant, including a biologic, was ineffective, not tolerated, or all are contraindicated.
- II. **Abrocitinib (Cibinqo)** may be considered medically necessary when the following criteria are met:
 - A. Criteria I(A) - I(B) above are met; **AND**
 - B. Treatment with dupilumab (Dupixent) and upadacitinib (Rinvoq) has been ineffective, contraindicated, or not tolerated.

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**

- III. The medication prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat atopic dermatitis or another auto-immune condition (e.g., Otezla/Otezla XR, Xeljanz, Olumiant); **AND**
- IV. Member has exhibited improvement or stability of disease symptoms (e.g., improvement in IGA score from baseline, BSA involvement, pruritis symptoms)

Supporting Evidence

- I. Atopic dermatitis (AD), also known as atopic eczema, is an inflammatory skin condition most frequently occurring in pediatric patients. It manifests with pruritis, dry skin, crusting, and serous oozing causing chronic scratching which leads to blister formation, skin thickening (lichenification), fissuring, or lesions. This condition is associated with elevated serum IgE and it is often a comorbid condition with asthma and allergic conditions.
- II. Treatments for mild-to-moderate AD include topical corticosteroids (TCS), topical calcineurin inhibitors (TCI), phototherapy, and/or crisaborole (Eucrisa) – a PDE4 inhibitor. Symptomatic treatments include oral and topical antihistamines and sleep aids for nighttime pruritus. Treatment choice between these products is dependent on severity, location, and other patient specific factors (e.g., allergies, age). According to AAD guidelines, TCIs may be preferable to TCS in patients with recalcitrance to steroids, sensitive areas involved, steroid-induced atrophy, and long-term uninterrupted topical steroid use.
- III. Treatment for moderate to severe disease not amenable to topicals includes systemic immunosuppressants (e.g., corticosteroids, cyclosporine, methotrexate, azathioprine, mycophenolate mofetil), JAK inhibitors (e.g., abrocitinib, upadacitinib), and dupilumab (Dupixent), a biologic IgG4 that is FDA-approved for pediatrics and adults as a biologic option for moderate-to-severe AD. Currently, there are no head to head trials evaluating safety and/or efficacy differences or superiority between biologic therapies in atopic dermatitis. Dupilumab (Dupixent) has an established safety and efficacy profile for the treatment of atopic dermatitis and is approved down to six years of age. Upadacitinib (Rinvoq) and abrocitinib (Cibinqo) have been evaluated and are FDA approved in patients down to 12 years of age.
- IV. There may be patient specific scenarios in which the use of additional topical agents following failure of one class of topical agents would be impractical. Insight from dermatology specialists indicate that patients who have at least 15% BSA involvement, or involvement in sensitive areas (e.g., eyelids, axilla, genitals, gluteal cleft), and have severe disease are potential candidates for systemic biologic therapy. Severe disease, as defined by NICE guidelines, includes widespread areas of dry skin, incessant itching, redness (with or without excoriation, extensive skin thickening, bleeding, oozing, cracking, and alteration of pigmentation), and severe limitation of everyday activities and psychosocial functioning, nightly loss of sleep; severe disease can also be classified as physician's global assessment (PGA) score of 4.0. Additionally, administration of topical agents may become impractical for patients with a high disease burden (BSA $\geq$ 20%), considering twice daily administration is necessary for non-steroid topical agents for optimal efficacy.
- V. Upadacitinib (Rinvoq) is FDA approved in patients with moderate to severe atopic dermatitis whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable. Similarly, abrocitinib (Cibinqo) is FDA approved in adults and pediatric patients 12 years of age and older with refractory, moderate-to-severe atopic dermatitis whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable. Due to safety

concerns, use of other systemic drugs is recommended prior to use of upadacitinib (Rinvoq) and abrocitinib (Cibinqo).

- VI. There is lack of head-to-head clinical trial data for the AD FDA-approved therapies, and superior safety and efficacy of any product cannot be confidently concluded. Thus, it is reasonable that pending no contraindication to therapy, preferred therapies be based on cost-effectiveness.

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Alopecia Areata

Initial Evaluation

- I. **Deuruxolitinib (Leqselvi), Ritlecitinib (Litfulo), or Baricitinib (Olumiant)** may be considered medically necessary when the following criteria are met:
 - A. Medication is prescribed by, or in consultation with, a dermatologist; **AND**
 - B. Medication prescribed will not be used in combination with biologics or other non-biologic specialty medications used to treat alopecia areata or another auto-immune condition (e.g., ruxolitinib (Opzelura), tofacitinib (Xeljanz), etc.); **AND**
 - C. A diagnosis of **alopecia areata (AA)** when the following are met:
 1. Member has severe alopecia areata as defined by $\geq 50\%$ scalp hair loss on the Severity of Alopecia Tool [SALT]; **AND**
 2. Current episode of alopecia areata lasting more than six months without spontaneous hair growth; **AND**
 3. Provider attestation that hair loss is not due to another condition such as male-pattern baldness (androgenic alopecia), secondary syphilis, tinea capitis, or trichotillomania, etc.; **AND**
 4. Treatment with a six-month trial of one of the following has been ineffective or not tolerated, unless all are contraindicated:
 - i. High-potency topical corticosteroids
 - ii. Intralesional corticosteroids
 - iii. Systemic therapy (e.g., oral corticosteroids, methotrexate, azathioprine, etc.)

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- iv. Topical immunotherapy [i.e., diphenylcyclopropenone (DPCP) or squaric acid dibutyl ester (SADBE)]; **AND**
- D. If the request is for **Olumiant 4 mg tablets**:
 - 1. Provider attestation that member did not respond adequately to treatment with Olumiant 2 mg tablets
- II. Deuruxolitinib (Leqselvi), ritlecitinib (Litfulo), and baricitinib (Olumiant) are considered investigational when used for all other conditions, including but not limited to:
 - A. Androgenic alopecia

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Medication prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat alopecia areata or another auto-immune condition (e.g., ruxolitinib (Opzelura), tofacitinib (Xeljanz), etc.); **AND**
- IV. Member has exhibited improvement or stability of disease symptoms (e.g., hair growth, improvement in the Severity of Alopecia Tool (SALT) score)

Supporting Evidence

- I. Deuruxolitinib (Leqselvi) and baricitinib (Olumiant) are FDA approved for severe alopecia areata (AA) in adults, and ritlecitinib (Litfulo) is approved in adolescents aged 12 years and older.
- II. Alopecia areata (AA) requires the care of a dermatologist due to the need for specialized and individualized care in those with AA. Hair loss can be caused by other health-related problems, such as hypothyroidism, certain mental disorders (i.e., trichotillomania), or hormone imbalances; therefore, a specialist is needed to properly diagnosis and treat patients.
- III. Alopecia areata (AA) is a chronic, immune-mediated disorder that targets hair follicles and causes nonscarring hair loss. The condition most commonly presents with discrete, smooth patches of alopecia on the scalp, but may also occur in other hair-bearing areas, such as the eyebrows, eyelashes, beard, and extremities. Spontaneous hair regrowth is common, and about 50% of patients with limited patchy hair loss will recover within a year. Alternatively, patients with moderate to severe AA (defined by a SALT score $\geq 20\%$) may have a chronic disease course with little to no remission periods. Alopecia areata (AA) is typically asymptomatic beside hair loss, but the social stigma and psychological effects are great, often impacting work and school life. Both genders, children, and adults may develop AA with peak onset in the third decade; however, the risk is increased in females and with older age. Alopecia areata (AA) affects up to 2% of the global population, with an estimated prevalence of one in 1,000 people in the United States (U.S.).
- IV. Severity of AA is evaluated by the absolute severity of alopecia tool (SALT) score. This score describes the percentage of scalp hair loss and ranges from 0 to 100. A SALT score of 100 means there is complete (100%) scalp hair loss, also called alopecia totalis (AT). A SALT score of 0 means there is no scalp hair loss. A SALT score of 50 or greater is considered severe disease. In 2020, the change in SALT score was validated by physicians and patients as to what value would

be the goal for clinical trials and considered to be the most clinically meaningful; this value was agreed to be achieving 20 or better, moving the patient to mild disease.

- V. Other AA assessment scorings focus on eyebrow/eyelash severity, such as the ClinRO measure for eyebrow hair loss (done at two feet away) and ClinRO for eyelash hair loss. Both ranked from 0-3 where zero equates to full coverage and there is no notable eyebrow/eyelashes. There are also a multitude of patient quality of life scores in AA as well. These include Scalp Hair Assessment, the PGI-I and the PGI-C, which are self-administered questionnaires ranking the improvement or worsening of the disease where one is greatly improved and seven is greatly worsened.
- VI. There is not a U.S. guideline for the treatment of AA. A consensus amongst international providers was published in the Alopecia Areata Consensus of Experts (ACE) (Meah, 2020) which includes one treatment paradigm. The American Academy of Dermatology (AAD) has unofficial guidelines noting that it is important to consider the positive and negative aspects of active treatment in AA. Some patients respond well, though treatment can be uncomfortable for the patient, time-consuming, and with undesirable side effects; therefore, leaving AA untreated is a legitimate option for many patients. Currently, the ACE study and the AAD website offer the most comprehensive recommendations for AA treatment.
- VII. Duration of hair loss, extent and area of hair loss, and patient age influence treatment choice in AA. All of the traditional therapies to date, outside of the JAK inhibitors, are not FDA approved for AA and have limited published data. The majority of evidence is based on case reports or case studies with a high variety of response rates, and tends to apply best for patients with patchy, limited hair loss. Multiple systematic review articles have been done in both the pediatric and adult patients, and while they do not clearly define place in therapy or sequential use of various products, the articles do recommend corticosteroids (oral, intralesional, topical) as first line due to the strongest level of efficacy from open-label, randomized clinical trials. The recommendations about subsequent lines of therapy are mixed. Although intralesional steroids are among the first modalities to be recommended, their use may be limited in young children and those with extensive disease due to painful administration. Additionally, systemic steroids may be favorable for acute AA but may not be appropriate for chronic AA due to safety considerations associated with long-term use. In pediatrics, contact immunotherapy has the second strongest level of evidence and oral agents, such as methotrexate, have not been studied in pediatric AA. Contact immunotherapy's level of evidence is primarily from case reports or case studies with a high variance of complete response results. Any of the off-label medications should be reassessed between the three- and six-month mark, as it may take three months for therapy to begin being effective, and treatment should continue past the terminal hair restoration. If there has been no hair growth at the six-month mark, treatment may be considered failed.
- VIII. Deuruxolitinib (Leqselvi), Ritlecitinib (Litfulo), and baricitinib (Olmiant) are second line treatments for patients with AA that fail to respond to first line interventions. Due to safety concerns, they should not be used in combination with another biologic.

Baricitinib (Olmiant)

- Baricitinib (Olmiant) was the first JAK inhibitor approved in June 2022 for AA. It was studied in two identical, double-blind, placebo-controlled, multicenter, Phase 3 clinical trials (BRAVE-AA1 and BRAVE-AA2). A total of 1,200 adult patients were randomized 2:3:2 to receive baricitinib (Olmiant) 2 mg (N=340) or 4 mg (N=515) or placebo (N=346) daily. All patients had at least 50% scalp hair loss at baseline. Patients were mainly female, 53% had complete/near-complete scalp hair loss, 69% had eyebrow hair loss, and 58% had eyelash hair loss. The average hair loss cycle

was four years with mean baseline SALT scores of 84-86. The primary endpoint was the number of patients achieving SALT ≤ 20 at week 36.

- BRAVE-AA1: 22.8% of 2 mg and 38.8% of 4 mg tablets versus 6.2% on placebo achieved SALT ≤ 20 . A treatment difference of 16.6 [95CI: 9.5, 23.8; $p < 0.001$] and 32.6 [25.6, 39.5; $p < 0.001$] respectively.
 - BRAVE-AA2: 19.4% on 2 mg and 35.9% on 4 mg versus 3.3% on placebo achieved SALT ≤ 20 . A treatment difference of 16.1 [9.1, 23.2; $p < 0.001$] and 32.6 [25.6, 39.6; $p < 0.001$] respectively.
- IX. Overall, between BRAVE-AA1 and BRAVE-AA2, baricitinib (Olumiant) 4 mg outperformed the 2 mg dose, and only the 4 mg tablets achieved statistical significance in the majority of the key secondary endpoints such as eyebrow/eyelash improvement, time to achieving SALT ≤ 20 .
- X. Long-term efficacy and safety data was reported in February 2024 after 104 weeks on baricitinib (Olumiant). Among baricitinib (Olumiant) 4-mg-treated and baricitinib (Olumiant) 2-mg-treated Week-52 responders, 90.7% and 89.2%, respectively, maintained SALT score ≤ 20 at Week 104 without new unknown safety signals.
- XI. In 2024, JAMA Dermatology published results from BRAVE-AA1 withdrawal and retreatment study. For the randomized withdrawal sub-study, patients initially randomized to baricitinib (Olumiant), 4 mg or 2 mg, who had achieved a SALT ≤ 20 at week 52, were rerandomized 3:1 to continue taking their current dose of baricitinib (Olumiant) or transition to placebo (randomized withdrawal). At week 52, 115 (41%) taking baricitinib (Olumiant) 4 mg, and 39 (21%) taking 2 mg had a SALT ≤ 20 and were eligible for randomized withdrawal. A total of 30/115 (26%) responders on baricitinib (Olumiant) 4 mg were transitioned to placebo and 10/39 (26%) of the baricitinib (Olumiant) 2 mg responders were transitioned to placebo. For patients who were withdrawn from baricitinib (Olumiant) 4 mg, 96% and 82% at weeks four and eight, respectively, maintained a SALT ≤ 20 . At week 152, only 6/30 (20%) patients had maintained that response. Similarly, for those withdrawn from baricitinib (Olumiant) 2 mg, 90% and 80% of patients, at weeks four and eight, respectively, maintained a SALT ≤ 20 and one patient (10%) maintained that response at week 152.
- XII. Baricitinib (Olumiant) is also being studied in patients aged six to seventeen years with severe or very severe AA and is estimated to be completed in Spring 2025.

Ritlecitinib (Litfulo)

- Ritlecitinib (Litfulo) was the second approved JAK inhibitor approved in June 2023. It was studied in a randomized, double-blind, placebo-controlled, multicenter, Phase 2b-3 trial (ALLEGRO) over 24 weeks. A total of 849 patients, aged 12 years and older, were randomized 2:2:2:2:1:1:1 to receive ritlecitinib (Litfulo) (N=718 total) daily or placebo (N=131). Multiple doses of ritlecitinib (Litfulo) were studied, but the FDA only approved daily use of 50mg (n=130) as reflected below. All patients had at least 50% scalp hair loss at baseline. Patients were mainly adults, White, 46% had total scalp hair loss, 83% had eyebrow hair loss, and 75% had eyelash hair loss. The average hair loss cycle was two and a half years with a mean baseline SALT scores between 88-93. The primary endpoint was the number of patients achieving SALT ≤ 20 at week 24.
 - At the end of the 24-week clinical program, ritlecitinib (Litfulo) 50mg (n=130) had 29 (23%) patients versus 2 (1.5%) on placebo achieving SALT ≤ 20 . A treatment difference of 21.85% [14.65, 30.23; $p < 0.001$] meeting statistical significance.
 - Key secondary endpoints such as the CGI-I scoring and regrowth of eyebrows/eyelashes also reached statistical significance.
- XIII. In August 2024, a post-hoc analysis reviewed ritlecitinib (Litfulo) for the impact on previous AA treatments and effects on efficacy. The post-hoc analysis grouped its results by topical, intralesional steroids (ILCS), topical immunotherapy, and oral immunosuppressants. Of the 522

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patients on ritlecitinib (Litfulo) during ALLEGRO, 360 (69%) had previous treatment: 266 (51%) topical steroids, 176 (34%) on systemic immunosuppressants, 134 (26%) ILCS, and 87 (17%) on contact immunotherapy. This post-hoc analysis noted that at week 24, patients previously treated with ILCS were more likely to have SALT ≤ 20 and less likely if treated with systemic immunosuppressants. However, at week 48, there was no difference to achieving SALT ≤ 20 .

- XIV. An interim analysis of the extension trial demonstrated that after 60 weeks of therapy, patients with $<95\%$ scalp hair loss at baseline reached median SALT scores of <2.4 and those with $\geq 95\%$ hair loss at baseline reached SALT scores between 10-20. Sustained response rates in both the SALT ≤ 20 and patient reported quality of life scores (PGI-C) were also seen at week 96.

Deuruxolitinib (Leqselvi)

- Deuruxolitinib (Leqselvi) was studied in two identical, multicenter, double-blind, placebo-controlled Phase 3 trials (THRIVE-AA1 and THRIVE-AA2). A total of 1,209 adult patients were randomized 5:3:2 to deuruxolitinib (Leqselvi) 8 mg (n=600) or 12 mg (N=342) twice daily or matching placebo (n=267.) The FDA did not approve the 12 mg dose due to adverse events that occurred in the extension phase trial. All patients had at least 50% scalp hair loss at baseline, majority were White, female, 58% had complete or near complete scalp hair loss, and 73% had eyebrow and/or eyelash hair loss. The average current hair loss cycle was four years with mean baseline SALT scores between 85-88. The primary endpoint was the number of patients achieving an absolute severity of alopecia tool (SALT) score of 20 or under at the end of 24-weeks.
 - In THRIVE-AA1: 94(29.6%) on 8 mg twice daily versus 1 (0.8%) on placebo achieved SALT ≤ 20 . A treatment difference of 28% [23,33; $p<0.001$]
 - In THRIVE-AA2: 77 (33%) on 8 mg twice daily versus 1 (0.8%) on placebo achieved SALT ≤ 20 . A treatment difference of 24% [19,30; $p<0.001$]
- XV. All key secondary endpoints achieved statistical significance over placebo, including patient satisfaction scores of “satisfied” or “very satisfied” on the hair satisfaction reported outcome (SPRO) scale and CGI-I.
- XVI. Post completion of the 24-week Phase 3 program, patients could enroll in the long-term extension, remaining on the 8 mg or 12 mg dose; however, after May 2023, all patients moved to the 8 mg dose due to thromboembolic events associated with the 12 mg dose. At week 68, 76.6% of those on 8 mg dose had a SALT ≤ 20 .

Evidence Summary

- XVII. Overall, the quality of evidence of deuruxolitinib (Leqselvi), ritlecitinib (Litfulo), and baricitinib (Olumiant) is moderate. All three medications were studied in Phase 3 clinical trials showing efficacy in their primary endpoint of achieving SALT ≤ 20 . This is clinically meaningful to patients with AA as it equates to having 80% of their scalp with active, restored hair growth. Additionally, the different clinical trial programs showed efficacy in their secondary endpoints, such as improvement in patient quality of life scorings and improvement in secondary hair loss sites measured by eyebrow/eyelash hair growth. Currently, ritlecitinib (Litfulo) is approved in those 12 years of age and older, baricitinib (Olumiant) is under investigation for those aged six through 17 years, and deuruxolitinib (Leqselvi) is beginning a study in adolescents with an estimated completion in 2026-2027.
- XVIII. The safety profile of deuruxolitinib (Leqselvi), ritlecitinib (Litfulo), and baricitinib (Olumiant) is similar to other JAK inhibitors on the market with headache, acne, nasopharyngitis, and upper respiratory tract infections being the most common adverse event experienced. All three agents share the same black box warning as other JAK inhibitors which include increased risk of serious infections, all-cause mortality, malignancy, thrombosis, and major adverse cardiac events. Malignancies occurred during the clinical trial programs of all three medications and baricitinib

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(Olumiant) was associated with a myocardial infarction. During long term studies, thromboembolic events and serious infections have occurred with the use of all three medications. Discontinuation rates for each medication due to an adverse event were low, baricitinib (Olumiant) at and ritlecitinib (Litfulo) at 1.5% and deuruxolitinib (Leqselvi) at 3.1%.

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Giant Cell Arteritis

Initial Evaluation

- I. **Upadacitinib (Rinvoq)** may be considered medically necessary when the following criteria below are met:
 - A. Member is being managed by, or in consultation with, a rheumatologist; **AND**
 - B. A diagnosis of **giant cell arteritis** when the following are met:
 1. Member is 18 years of age or older; **AND**
 - i. A diagnosis of **giant cell arteritis** positively confirmed by one of the following:
 - a. Temporal artery biopsy
 - b. Doppler ultrasound
 - c. Magnetic resonance angiography (MRA)
 - d. Positron emission tomography (PET)

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Member has exhibited improvement or stability of disease symptoms; **AND**
- IV. Agent prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat giant cell arteritis or another auto-immune condition (e.g., Otezla/Otezla XR, Xeljanz, Olumiant, etc.)

Supporting Evidence

- I. Giant cell arteritis (GCA) is an inflammatory vascular condition that is most frequently occurring in adult patients 50 years of age or older. It manifests with fever, fatigue, headache, transient or permanent vision loss, and large vessels involved like the aorta, and major vessels in upper extremities. Large vessel involvement includes dissections, aneurysm, tenderness to palpation, or asymmetric blood pressure. This condition is associated with elevated serum ESR and CRP levels and it is often closely related to polymyalgia rheumatic disease.
- II. In 2022 ACR/EULAR came out with updated classification criteria for giant cell arteritis. These criteria have demonstrated a sensitivity of 87% and a specificity of 94.8%. Current ACR guidelines are from 2021, therefore this new classification criteria are not included in the most current guidelines.
- III. The 2021 American College of Rheumatology guidelines for GCA recommends starting high dose daily glucocorticoids, or tocilizumab with glucocorticoids or tocilizumab alone in newly diagnosed GCA. Patients with active extracranial large vessel involvement OR disease relapse with symptoms of cranial ischemia may start tocilizumab and glucocorticoids or start methotrexate with glucocorticoids if tocilizumab is not an option due to cost or tolerability. Guidelines have not been updated to include upadacitinib (Rinvoq).
- IV. Upadacitinib (Rinvoq) is FDA approved for adults with GCA based off results of a Phase 3 RCT (SELECT-GCA). In this trial 428 patients were randomized to oral upadacitinib (Rinvoq) plus a prednisone taper or placebo plus a prednisone taper. The primary outcome of glucocorticoid-free remission was statistically significant, with 46% in the upadacitinib (Rinvoq) 15 mg group compared to 29% in the placebo group (17% treatment effect, $p = 0.002$). The safety profile of upadacitinib (Rinvoq) is similar to what is seen with other indications.
- V. Tocilizumab (Actemra) is FDA-approved for adult patients with giant cell arteritis based off results of a phase 3 RCT. In this trial, 251 patients were randomized to subcutaneous tocilizumab plus a prednisone taper or placebo plus a prednisone taper. The primary outcome of glucocorticoid-free remission was statistically significant, with 53% and 56% (weekly and every other week dosing, respectively) of tocilizumab patients having sustained remission at week 52, compared to 14% and 18% (26-week versus 52-week taper, respectively) of prednisone patients ($p < 0.001$).
- VI. Although upadacitinib is an FDA-approved medication for GCA, tocilizumab (Actemra) has equal or greater safety and efficacy data to support its use in this condition. There are also no current head-to-head trials comparing upadacitinib (Rinvoq) to tocilizumab (Actemra) in GCA. Guidelines have consensus regarding the use of tocilizumab (Actemra); however, there is no consensus on the use of upadacitinib (Rinvoq) due to the newer approval.

VII. Standard dosing of upadacitinib (Rinvoq) for GCA is 15 mg once daily.

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Investigational or Not Medically Necessary Uses

- I. Combination use with topical and systemic JAK inhibitors
 - A. The safety profile of systemic JAK inhibitors is continuing to develop; however, the FDA has issued cardiovascular and malignancy warnings. The true safety profile of ruxolitinib is unknown at this time, given the short trial duration and relatively small trial population. Utilizing a systemic JAK therapy in addition to topical JAK therapy (ruxolitinib) has unknown, and potentially additive, risks. Until further data are available to establish a safety profile with this combination, dual use will be disallowed.
- II. COVID-19 or associated symptoms or complications
 - A. The role of JAK-inhibitors in the treatment of COVID-19 is evolving and varies among available guidelines. Long-term data is not available and continuing therapy beyond hospitalization has not been evaluated for safety and efficacy.
- III. Various dermatologic conditions (including, but not limited to plaque psoriasis, guttate psoriasis, vitiligo, dermatomyositis, lichen planus)
 - A. Case reports suggest that the use of TNF inhibitors may induce flares when used for guttate psoriasis. Typical treatment involves phototherapy and topical corticosteroids/vitamin D analogs, with tonsillectomy or antibiotics used for more refractory disease. There is no established efficacy data for the use of biologics, JAK inhibitors, or targeted DMARDs in this setting at this time.
 - B. A systematic review by Ciechanowich et al. evaluated the use of JAK inhibitors in psoriasis, atopic dermatitis, and vitiligo. Seventeen studies (11 randomized controlled trials, 4 case reports, 1 retrospective case series, and 1 open-label clinical trial) were included in the review and concluded that there is limited data to suggest the safety and efficacy of JAK inhibitors in various dermatologic diseases outside of FDA-approved indications. As of November 2022, deucravacitinib (Sotyktu) is the only JAK inhibitor FDA-approved to treat plaque psoriasis; upadacitinib (Rinvoq) and abrocitinib (Cibinqo) are FDA-approved to treat atopic dermatitis.
- IV. Atopic Dermatitis – Olumiant (baricitinib)
 - A. Two phase III, double-blind, multicenter monotherapy trials BREEZE-AD1 and BREEZE-AD2 studies concluded baricitinib 2mg, 4mg reached its primary endpoint of Validated Investigator's Global Assessment at week 16 compared to placebo. The manufacturer reports a statistical improvement in Investigator's Global Assessment (IGA) scores at week 16 compared to placebo, baricitinib improved clinical signs and symptoms in patients with moderate-to-severe AD within 16 weeks of treatment and induced rapid reduction of itch. The safety profile remained consistent with prior findings from baricitinib clinical development in AD, with no new safety concerns. The drug remains in clinical

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development and is considered experimental and investigational at this time. Three clinical trials are currently ongoing which may provide further confirmation of safety and efficacy.

V. Familial Mediterranean Fever

- A. Current studies for Familial Mediterranean Fever, a subgroup of periodic fever syndrome, are limited to case reports. In evaluating current evidence available, quantitative evaluation of response to biologic treatments (e.g., tocilizumab, infliximab, etanercept, adalimumab, anakinra and canakinumab) is difficult to obtain, and therefore, difficult to assess true efficacy and safety. In the absence of controlled studies to evaluate the safety and efficacy of biologics in the treatment of patients with Familial Mediterranean Fever, the use of biologics in this setting would be considered experimental and investigational.

VI. Lupus Nephritis, Systemic Lupus Erythematosus (SLE), and Cutaneous Lupus Erythematosus (CLE)

- A. In a 24-week phase II RCT evaluated baricitinib in adults with highly active SLE exhibiting skin and joint symptoms despite the standard treatment, 314 patients were randomly assigned to receive placebo, baricitinib 2 mg, or baricitinib 4 mg. At week 24, baricitinib 4 mg dose ($p=0.0414$), but not the 2 mg dose, improved the signs and symptoms of active SLE. The short follow-up/study design limits the findings from this study.
- B. Lilly and Incyte have decided to end lupus development for Olumiant (baricitinib) after receiving topline efficacy data from two Phase III studies (SLE-BRAVE 1 and SLE-BRAVE 2) in adults with active lupus. While Olumiant (baricitinib) reached the primary endpoint in one trial (SLE-BRAVE 1), follow up trial (SLE-BRAVE 2) failed to meet the primary endpoint and neither trial achieved key secondary endpoints.

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy	Disease state
Chronic Inflammatory Disease Policy	Rheumatoid Arthritis
	Polyarticular Juvenile Idiopathic Arthritis (PJIA)
	Enthesitis-Related Arthritis (ERA)
	Systemic Juvenile Idiopathic Arthritis (SJIA)
	Psoriatic Arthritis
	Ankylosing Spondylitis
	Non-radiographic Axial Spondyloarthritis
	Plaque Psoriasis
	Crohn's Disease
	Ulcerative Colitis
	Behcet's Disease (i.e., Behcet Syndrome)
	Hidradenitis Suppurativa
	Uveitis and Panuveitis
	Giant Cell Arteritis
	Tumor Necrosis Factor Receptor-Associated Periodic Syndrome (TRAPS)
	Familial Mediterranean Fever
	Hyperimmunoglobulin D Syndrome/Mevalonate Kinase Deficiency (HIDS/MKD)
	Cryopyrin-Associated Periodic Syndromes (CAPS)
	Recurrent Pericarditis
	Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD)
	Polymyalgia Rheumatica
ruxolitinib (Jakafi, Opzelura) Policy	Intermediate or high-risk myelofibrosis
	Polycythemia vera
	Graft-Versus-Host Disease
	Atopic dermatitis
fedratinib (Inrebic) Policy	Myelofibrosis

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Dupilumab (Dupixent) Policy	Atopic dermatitis
Tralokinumab (Adbry) Policy	Atopic dermatitis
Tapinarof (Vtama) Policy	Plaque psoriasis
Nemolizumab (Nemluvio) Policy	Atopic Dermatitis
Lebrikizumab (Ebglyss) Policy	Atopic Dermatitis
Spesolimab SC (Spevigo) Policy	Generalized pustular psoriasis (GPP)

Policy Implementation/Update

Action and Summary of Changes	Date
Added Otezla XR to the policy	10/2025
Live 07/01/2025: Stelara moved to non-preferred. Addition of select ustekinumab biosimilars (Selarsdi, Steqeyma, and Yesintek) to preferred. Added criteria for Rinvoq for treatment of GCA.	06/2025
Removed age limitations from policy criteria	02/2025
Live 01/01/2025: Addition of tocilizumab-aazg (Tyenne) as a preferred product. Addition of alopecia areata coverage criteria, original criteria presented at P&T; 12/2024 update requiring provider attestation that member did not respond adequately to treatment with Olumiant 2 mg tablets when requesting an increase to 4mg tablets.	12/2024
Change to Ankylosing Spondylitis (AS) and Non-radiographic Spondyloarthritis (nr-axSpA) criteria to remove requirements for disease manifestation as axial or peripheral arthritis, change to definition of high disease activity, change to supportive evidence sections. Updated related policies.	11/2024
Live 8/01/2024: addition of upadacitinib (Rinvoq) for age expansion to two years of age and older for psoriatic arthritis and a new approval for PJIA. Also included addition of new solution product.	7/2024
Live 04/01/2024: addition of select biosimilars (Hadlima and adalimumab-adaz) as preferred products, removal of brand Humira as a preferred product. Change to ulcerative colitis criteria to require trial of at least one corticosteroid or immunomodulator; change to Crohn's disease criteria to require trial of at least one corticosteroid or immunomodulator and change to define high-risk Crohn's disease and remove severe Chron's disease	02/2024
Live 01/2024: Added guselkumab (Tremfya) as a preferred product.	11/2023
Updated Cibinqo age requirements. Update to supporting evidence.	04/2023
Live 06/2023: Added criteria to include new indication for Rinvoq in the setting of Crohn's disease. Updated quantity limit table to include new indication of Crohn's disease for Rinvoq. Updated initial authorization for Rinvoq XR 45mg tablets to two months for Ulcerative Colitis and three months for Crohn's disease, added fill limit of three fills per year for CD. Updated supporting evidence section and references for Crohn's disease.	03/2023
Review conducted. Update to supporting evidence.	02/2023
Effective 01/01/2023 - Cibinqo in setting of atopic dermatitis: updated to require trial of Dupixent AND Rinvoq, previously only listed Rinvoq	12/2022
Added criteria to include new indication for Rinvoq in the setting at non-radiographic spondyloarthritis. Updated supporting evidence and references for AS and nr-axSpA sections. Updated wording of renewal criteria regarding combination biologic use to reflect specific disease state referenced. Updated E/I supporting evidence for use of JAK inhibitors in dermatologic conditions. Updated related policies section.	11/2022
Addition of new molecular entity, Sotyktu in plaque psoriasis	08/2022
Added new indication for Rinvoq in the setting of active ankylosing spondylitis, updated supportive evidence, and reference section. Added new indication of alopecia areata for baricitinib (Olumiant®) noting this is an excluded indication.	06/2022
Added Rinvoq's new indication of Ulcerative Colitis, updated supporting evidence section; added new criteria for Rinvoq in the setting of Atopic Dermatitis to require use of systemic immunosuppressants, including biologic agents first to align per label; added Olumiant's indication of COVID-19 and new tablet strength in the QL table; removed AS from E/I section given recent FDA-approval of Rinvoq in AS; updated formatting.	05/2022
Added Cibinqo for the setting of Atopic Dermatitis, built out the Atopic Dermatitis criteria section in the policy for Cibinqo and Rinvoq with new FDA approvals. Updated PJIA supporting evidence and references to further clarify guidelines and treatment algorithm and align with Chronic Inflammatory Disease policy.	03/2022
Added new indications for Rinvoq in setting of PsA and Xeljanz in AS. Updated AS supporting evidence and references to include 2019 guideline update. Added criteria for all diagnoses requiring trial of TNF blockers prior to JAK inhibitor therapy as recommended by FDA labeling. Experimental and investigational	02/2022

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section updated to include warning on combination of topical and oral JAK inhibitors and alopecia areata. Added new Rinvoq 30mg tablet availability for atopic dermatitis.	
Created the Janus Associated Kinase Inhibitor policy. Added Rinvoq and Xeljanz to preferred product mix (effective 1/1/2022). Added Related Policies section.	12/2021
Previous policy changes (relevant from Chronic Inflammatory Policy)	
Updated criteria for ulcerative to modify the weight requirement for Humira to a specific age group. Added a requirement to try and fail TNF blockers before allowing treatment with tofacitinib (Xeljanz) as recommended by FDA labeling. Supporting evidence and references updated.	06/2021
Updated PA policy to include FDA approvals for Xeljanz for PJIA. Updated supporting evidence section with clinical trial data	11/2020
Updated the products for psoriatic arthritis to include guselkumab (Tremfya). Updated the supporting evidence section for psoriatic arthritis to reflect no changes in the guidelines with regard to guselkumab (Tremfya).	08/2020
Criteria updated to new policy format. Specific changes include: <u>Rheumatoid Arthritis</u> - Removed the number of joints and duration of disease question as evidence and guidelines did not support the requirement - Removed requirements for diagnosis due to varying methods to diagnose and limited value of this question from health plan standpoint - Clarified use of oral DMARD requirement may be bypassed if all of them are contraindicated - Added newly approved upadacitinib (Rinvoq) as a non-preferred alternative <u>Polyarticular Juvenile Idiopathic Arthritis (PJIA)</u> - Removed the number of joints and duration of disease question as evidence and guidelines did not support the requirement - Added route to approval of Actemra as Actemra was previously in a separate policy <u>Psoriatic Arthritis</u> - Added requirement of the presence of active severe disease and provided specific indicators of severe disease - Added clinical note: "If a patient has a diagnosis of both plaque psoriasis and psoriatic arthritis, approval of the requested medication can be made as long as the patient fulfills the criteria for at least one of the disease states and associated medication criteria." <u>Ulcerative Colitis</u> - Added age of 18 years or older - Addition of trial of thiopurine for at least 8 weeks	08/2019
Criteria update: Increased initial approval from 3 months to 6 months, updated initial QL to reflect 6 month approval duration. Added new Xeljanz IR 10mg tablet availability. Added baricitinib (Olumiant) as an option for the treatment of rheumatoid arthritis after trial and failure of a TNF antagonist.	07/2018
Criteria update: Added new Kevzara auto injector formulation, Xeljanz new indication in ulcerative colitis, added Cimzia new indication in plaque psoriasis, minor formatting edits.	06/2018
New Criteria Set – consolidated from all biologic agents along with Otezla/Otezla XR and Xeljanz criteria sets. Within this new criteria set, here are the following updates: 18 years of age requirement has been removed for Stelara as it has now been FDA approved for pediatric plaque psoriasis. - New FDA approved indication of psoriatic arthritis has been added for Xeljanz/Xeljanz XR and Taltz - The question regarding dual therapy has been refined to encompass the language of biologics and other non-biologics (e.g. Otezla/Otezla XR and Xeljanz). - The question regarding DMARDs has been refined to only include agents that are administered non-biologic, non-specialty and that are administered orally. - For the indication of plaque psoriasis, the question addressing the trial of UVB has been combined with the trial of DMARDs.	01/2018

Policy Type: PA

Pharmacy Coverage Policy: UMP065

Split Fill Management*

Description

Talazoparib (Talzenna) is an orally administered poly (ADP-ribose) polymerase (PARP) inhibitor.

Length of Authorization

- Initial: Three months
- Renewal: Twelve months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
talazoparib (Talzenna)	Breast cancer, locally advanced or metastatic, BRCA-mutated	0.1 mg capsules	30 capsules/ 30 days*
		0.25 mg capsules	
		0.3 mg capsules	
	Prostate cancer, metastatic castration-resistant, homologous recombination repair (HRR) gene-mutated	0.5 mg capsules	
		0.75 mg capsules	
		1 mg capsules	

* Quantity limit exceptions are limited to dose reductions and clinician review

Initial Evaluation

- I. **Talazoparib (Talzenna)** may be considered medically necessary when the following criteria below are met:
 - A. Member is 18 years of age or older; **AND**
 - B. Medication is prescribed by, or in consultation with, a specialist in oncology; **AND**
 - C. Member has not had disease progression on prior PARP inhibitor therapy (e.g., niraparib [Zejula], rucaparib [Rubraca], olaparib [Lynparza]); **AND**
 - D. A diagnosis of **locally advanced (stage III) or metastatic (stage IV) breast cancer** when the following are met:
 1. Medication will be used as monotherapy; **AND**
 2. Documented deleterious (pathogenic) or suspected deleterious (likely pathogenic) germline BRCA mutation as determined by FDA approved diagnostic testing; **AND**
 3. Prior treatment with an anthracycline (e.g., doxorubicin) and/or a taxane (e.g., paclitaxel) was ineffective, unless contraindicated; **AND**
 4. For hormone receptor-positive (ER/PR+) disease, member has had disease progression on endocrine therapy; **OR**
 - i. Endocrine therapy has been deemed inappropriate by the treating healthcare provider
 - E. A diagnosis of **metastatic, castration-resistant prostate cancer (mCRPC)**; **AND**

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1. Evidence of disease progression despite therapy with a gonadotropin-releasing hormone analog (GnRH) or bilateral orchiectomy; **AND**
 2. The member has not had disease progression on a second-generation antiandrogen agent (e.g. abiraterone, enzalutamide (Xtandi), apalutamide (Erleada), darolutamide (Nubeqa)); **AND**
 3. Talazoparib (Talzenna) will be used in combination with enzalutamide (Xtandi); **AND**
 4. Documentation of deleterious (pathogenic) or suspected deleterious (likely pathogenic) alteration in the BRCA1 or BRCA2 gene; **AND**
 - i. Documentation of intolerance or contraindication to generic abiraterone in combination with olaparib (Lynparza) (use of generic abiraterone 250 mg tablets required); **OR**
 5. The member has an alteration in an HRR gene that is not BRCA1 or BRCA2 (e.g., ATM, ATR, CDK12, etc.)
- II. Talazoparib (Talzenna) is considered investigational when used for all other conditions, including but not limited to:
- A. When used in combination with any other chemotherapy or targeted therapy
 - B. Early-stage breast cancer
 - C. Ovarian cancer, fallopian tube, and peritoneal cancer
 - D. Lung cancer
 - E. Prostate cancer, non-metastatic, castration-sensitive, and without HRR mutation

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Clinical documentation of response to treatment (e.g., stabilization of disease, decrease in tumor size or tumor spread, lack of disease progression); **AND**
 - A. **Locally advanced (stage III) or metastatic (stage IV) breast cancer;**
 1. Talazoparib (Talzenna) will not be used in combination with other anti-cancer agents (outside of gonadotropin releasing hormone agonist [e.g., leuprolide], endocrine therapy [e.g., anastrozole, tamoxifen, fulvestrant]; **OR**
 - B. **Metastatic, castration-resistant prostate cancer (mCRPC);**
 1. Talazoparib (Talzenna) will be used in combination with enzalutamide (Xtandi)

Supporting Evidence

Breast Cancer

- I. Talazoparib (Talzenna) is FDA-approved for the treatment of adults with germline BRCA mutated (gBRCAm), HER2-negative, locally advanced or metastatic disease.
- II. The efficacy and safety of talazoparib (Talzenna) monotherapy was demonstrated in an open-label randomized, trial (EMBRACA) which enrolled adult patients that had a deleterious or suspected deleterious germline BRCA1/2 mutation detected by testing with BRACAnalysis.

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- III. Overall, 431 patients were randomized 2:1 to receive talazoparib or chemotherapy of the provider's choice (capecitabine, eribulin, gemcitabine or vinorelbine); 287 patients received talazoparib and 144, chemotherapy. Baseline characteristics of both groups were generally similar, but the talazoparib included a higher number of patients with a baseline Eastern Cooperative Oncology Group (ECOG) performance score of 1 or 2 and a higher number of patients whose disease progressed to advanced within 12 months of initial diagnosis.
- IV. To be included in the EMBRACA study, patients had received no more than three previous cytotoxic regimens for advanced breast cancer, and they had received previous treatment with a taxane or an anthracycline, or both, unless contraindicated. Additionally, previous neoadjuvant or adjuvant platinum-based therapy was allowed, provided the patient had a disease-free interval for at least six months after the last dose. Patients were excluded if they had disease progression while receiving platinum chemotherapy for advanced breast cancer (i.e., progression of disease within approximately eight weeks after the last dose). Third, patients included in the study had no more than three prior therapies in the advanced breast cancer setting. More than two therapies in other settings (e.g. neoadjuvant, adjuvant) do not apply. However, as current guidelines move to testing for targeted therapies once diagnosed, the likelihood of patients using over one line of therapy is rare.
- V. The primary endpoint of the study was radiologic progression-free survival (PFS) done via imaging at baseline, every 6 weeks until week 30, and then every 9 weeks after. The median progression-free survival was significantly longer among patients in the talazoparib group than among patients in the standard-therapy group (8.6 months [95% confidence interval {CI}, 7.2 to 9.3] vs. 5.6 months [95% CI, 4.2 to 6.7]; hazard ratio for disease progression or death, 0.54; 95% CI, 0.41 to 0.71; P<0.001).
- VI. Although prior endocrine-based therapy was not required in the EMBRACA trial, 90.4% of patients had progressed on endocrine-based therapy before being treated with talazoparib (Talzenna), and 100% had received prior chemotherapy for HR+ disease. The standard treatment approach for HR+ disease is to first target the hormone pathway (unless considered inappropriate), then consider single agent chemotherapy or PARP inhibitor if there is a progression on endocrine-based therapy.
- VII. The National Comprehensive Cancer Network (NCCN) breast cancer guideline lists the PARP inhibitors [talazoparib (Talzenna) and olaparib (Lynparza)] as Category 1 options for previously treated recurrent or metastatic germline BRCA mutated breast cancer. EMBRACA clinical program included 56% patients with ER/PR+, HER2- advanced or metastatic breast cancer, while 44% had triple-negative breast cancer (TNBC). Thus, talazoparib (Talzenna) may be considered a practical treatment option for patients with TNBC. However, presence of germline BRCA1 or BRCA2 mutation is a pre-requisite for initiating treatment with talazoparib (Talzenna).
- VIII. In the EMBRACA trial, adverse reactions were reported at a higher incidence in those receiving talazoparib than placebo-chemotherapy arm. Sixty-five percent of patients taking talazoparib versus 50% chemotherapy experienced ADE and dose reductions due to any cause occurred in 53% of talazoparib patients versus chemotherapy patients. Due to the high incidence of this, split fill is applied to the medication upon initial approval.
- IX. Dose adjustments are common with talazoparib (Talzenna) and the as the product it is flat priced (i.e., there is a single fixed price for *each* tablet regardless of dosage strength). When

possible, patients should be dose optimized to once a day dosing of an appropriate strength versus allowing multiple tablets of a lower dose.

Prostate Cancer

- I. Talazoparib (Talzenna) is FDA approved for the treatment of metastatic castration resistant prostate cancer (mCRPC) with HRR-gene mutation.
- II. The safety and efficacy of talazoparib (Talzenna) is demonstrated in the TALAPRO-2 trial, which is a randomized, double blind, placebo-controlled, phase 3 trial. Eight hundred and five patients were randomized 1:1 to either receive enzalutamide in combination with talazoparib (Talzenna) or placebo. They were further stratified by previous novel hormonal therapy/docetaxel and HRR gene-alteration status. The primary outcome was radiographic progression free survival (rPFS) assessed by blinded independent central review per RECIST 1.1 (soft tissue disease) and Prostate Cancer Clinical Trials Working Group 3 (bone disease). Treatment with talazoparib/enzalutamide resulted in a 37% lower risk of radiographic progression or death compared to placebo/enzalutamide (HR 0.63; 95% CI 0.51–0.78; $p < 0.0001$). The most common adverse effects in the treatment group were anemia (66%), neutropenia (36%), and fatigue (34%).
- III. One of the key inclusion criteria in TALAPRO-2 was bilateral orchiectomy or ongoing ADT with a GnRH agonist/antagonist. ADT was required to be continued throughout the study for patients who had not undergone bilateral orchiectomy. The safety and efficacy of Talzenna/enzalutamide in patients with prior treatment and progression on a second-generation AR inhibitor (i.e., enzalutamide, apalutamide and darolutamide) has not been established as these patients were excluded from the trial.
- IV. The PROpel trial investigating Lynparza versus placebo in combination with abiraterone targeted a similar patient population as TALAPRO-2, men with metastatic castration resistant prostate cancer with HRR related mutations. The treatment group demonstrated a reduced risk of disease progression or death by 34% versus abiraterone alone (HR 0.66; 95% CI 0.54-0.81; $p < 0.0001$). As of August 2023, head-to-head trials have not been conducted to suggest superiority of one regimen over the other. Abiraterone is currently available as a generic formulation. Lynparza/abiraterone was FDA approved for this indication in patients harboring a *BRCAm*, while Talzenna/enzalutamide carries a broader FDA approval encompassing all *HRRm* (e.g., ATM, ATR, CDK12, etc.)
- V. DNA repair anomalies known as homologous recombination repair gene mutations (HRRm) are identified in approximately 25% of patients with mCRPC. HRR gene mutations can consist of mutations in *ATM*, *ATR*, *BRCA1*, *BRCA2*, *CDK12*, *CHEK2*, *FANCA*, *MLH1*, *MRE11A*, *NBN*, *PALB2*, or *RAD51C*. Approximately 10-15% of patients with mCRPC have the BRCA1/BRCA2 gene mutations. These mutations have been associated with more aggressive disease and poor patient outcomes.

Investigational or Not Medically Necessary Uses

- I. The efficacy and safety of talazoparib (Talzenna) in combination with other chemotherapy or immunotherapy agents have not been evaluated. Talazoparib (Talzenna) is indicated as monotherapy.
- II. There is no evidence to support the use of a subsequent PARP inhibitor following the progression of disease on another PARP inhibitor.

- III. Due to its mechanism of action, there is interest in using talazoparib (Talzenna) in other cancers such as ovarian cancer, and lung cancer; however, studies are still ongoing and use outside of BRCA mutated advanced or metastatic breast cancer is considered investigational.
- IV. Additionally, there is a lack of evidence supporting the use of talazoparib (Talzenna) in early breast cancer (e.g., neoadjuvant or adjuvant treatment).

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

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Related Policies

Policy Name	Disease state
Cyclin-Dependent Kinase (CDK) 4/6 Inhibitors	Breast cancer, HER2-negative, HR-positive, advanced or metastatic, early-stage breast cancer
alpelisib (Piqray)	PIK3CA mutation, HR+, HER2-, advanced or metastatic breast cancer
lapatinib (Tykerb)	Breast cancer, HER2 over expression, advanced or metastatic in combination with capecitabine after prior therapy OR postmenopausal women, in combination with letrozole
neratinib (Nerlynx)	Breast cancer, early stage, HER2-positive, following trastuzumab OR advanced, metastatic
olaparib (Lynparza)	Breast cancer, metastatic, HER2-negative, germline BRCA-mutated (gBRCAm) Prostate cancer, metastatic castration-resistant (mCRPC)
tucatinib (Tukysa)	Metastatic breast cancer
Second Generation Anti-Androgen Agents	Prostate cancer

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated step through Lynparza/abiraterone for mCRPC to delineate between patients with BRCAm vs HRRm; updated supporting evidence	02/2024
Added expanded indication for the treatment of mCRPC in combination with enzalutamide; updated supporting evidence	09/2023
Streamlined clinical criteria to better reflect our current PARP policies. Removed requirement of HER2 negative disease. Removed confirmation member is not platinum refractory. Removed requirement of maximum number of prior cytotoxic regimens. Improved supporting evidence section for better clinical support. Added related policies.	08/2022
Previous Reviews	02/2019

Policy Type: PA

Pharmacy Coverage Policy: UMP262

Description

Tapinarof (Vtama) cream is a topical aryl hydrocarbon receptor agonist.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
tapinarof (Vtama)	Atopic Dermatitis	1% topical cream	60 grams/30 days
	Plaque Psoriasis		

Initial Evaluation

- I. **Tapinarof (Vtama) cream** may be considered medically necessary when the following criteria are met:
 - A. The request is for treatment of **Plaque Psoriasis; AND**
 1. Member is 18 years of age or older; **AND**
 2. Treatment with at least one agent from three different topical medication classes below has been ineffective or not tolerated, unless all are contraindicated:
 - i. Corticosteroid: High-potency corticosteroid (e.g., betamethasone, clobetasol)
 - a. When located on the face or intertriginous areas only, low-potency corticosteroid (e.g., hydrocortisone) accepted
 - ii. Calcineurin inhibitor: tacrolimus ointment or pimecrolimus cream
 - iii. Vitamin D analog: calcipotriene cream/ointment or calcitriol ointment
 - iv. Retinoid: tazarotene cream; **OR**
 - B. The request is for treatment of **Atopic Dermatitis; AND**
 1. Member is 2 years of age and older; **AND**
 - i. Treatment with ruxolitinib (Opzelura) has been ineffective, contraindicated, or not tolerated for those 12 years and older with mild to moderate disease; **AND**
 2. Treatment with at least one agent from two of the following groups has been ineffective, contraindicated, or not tolerated:
 - i. Group 1: topical corticosteroids (e.g., hydrocortisone, desonide, triamcinolone, betamethasone, clobetasol)
 - ii. Group 2: topical calcineurin inhibitors: tacrolimus (e.g., Protopic), pimecrolimus (e.g., Elidel)
 - iii. Group 3: topical phosphodiesterase 4 inhibitor: crisaborole (Eucrisa)

- II. Tapinarof (Vtama) is considered investigational when used for all other conditions, including but not limited to:
 - A. Plaque psoriasis in pediatric or adolescent patients
 - B. Cutaneous Lupus Erythematosus

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Member has exhibited improvement or stability of disease symptoms (e.g., improvement in IGA score from baseline, reduction in BSA involvement, pruritis symptom reduction)

Supporting Evidence

- I. Tapinarof (Vtama) cream is a non-steroidal topical medication for the treatment of plaque psoriasis and atopic dermatitis (AD). Coverage consideration is limited to those 18 years of age or older for plaque psoriasis those aged two and over for atopic dermatitis.
- II. Tapinarof (Vtama) cream is being evaluated in clinical trials for other skin conditions (e.g., cutaneous lupus); however, safety and efficacy have not been sufficiently demonstrated for any condition other than plaque psoriasis and atopic dermatitis. Due to the differing diagnoses and management strategies, use should be done with, or in consultation with, a dermatologist.

Plaque Psoriasis

- I. Tapinarof (Vtama) cream joins a market of well-established, effective, and generic topical treatment options for psoriasis:
 - Topical corticosteroids (TCS) are the mainstay of therapy for plaque psoriasis, with a variety of chemical entities, potencies, and formulations to satisfy patient needs. These are highly effective, and safety concerns or adverse events can be mitigated by proper use (i.e., application to affected areas only), use of products that offer appropriate potency for extent/severity/area of the body, and the correct formulation (e.g., foams, sprays, oils, or shampoos for scalp involvement). Plaque psoriasis on the face or intertriginous areas may require a low potency TCS (e.g., OTC hydrocortisone 1%). Skin atrophy is a common concern for utilizing TCS for extended durations of time; however, this is rarely a concern when TCS are applied to plaques appropriately (e.g., on active current lesions). For patients that experience quick recurrence of plaques after TCS discontinuation, TCS may be restarted intermittently, or steroid-sparing therapy may be considered, which may have synergistic effects with TCS.
 - Topical calcineurin inhibitors (TCI): Tacrolimus 0.1% ointment and pimecrolimus 1% cream are the available generic TCI products, and they may be utilized as monotherapy or in combination with other topicals. These are safe and effective and have been evaluated for use on the face and intertriginous areas, as well as, in pediatric patients.
 - Vitamin D analogs: Calcipotriene and calcitriol are the available generic products, and they may be utilized as monotherapy or in combination with other topicals. Combination use with TCS may have synergistic efficacy and increase tolerability vs.

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either agent alone. Monotherapy preparations are available, as well as betamethasone dipropionate-calcipotriene as a generic single preparation combination therapy as various formulations. These are applied once daily.

- Topical retinoid: Tazarotene 0.05% cream and 0.1% cream and foam are available with the 0.1% products being available as generics. Similar to vitamin D analogs, use with TCS may increase improve efficacy and tolerability. A single preparation combination therapy is available for halobetasol-tazarotene (Duobrii).
- II. Tapinarof (Vtama) cream has not proven to be superior in safety or efficacy to established therapies. Given the lack of definitive clinical advantage, and higher cost relative to available therapies, required use of at least three different classes of standard of care topical medications and ruxolitinib (Opzelura) is clinically appropriate and cost effective.
- III. Tapinarof (Vtama) cream was evaluated as monotherapy in two Phase 3, randomized, blinded, vehicle-controlled clinical trials (PSOARING 1 and 2), which showed improvement in extent and severity of psoriasis as well as improvement in patient quality-of-life vs. a placebo vehicle. It was effective and well tolerated when used on the face and intertriginous areas. The extent of efficacy as well as safety when used in combination with other topical or systemic agents for this condition are currently unknown given the use as monotherapy only in clinical trials.
- IV. The long-term efficacy trial, PSOARING 3, was open to those patients on either tapinarof (Vtama) or vehicle from PSOARING 1 or 2, that completed the 12 weeks. All patients were eligible for 40 weeks of open label therapy on tapinarof (Vtama); treatment was based on the PGA score. Patients entering with $\text{PGA} \geq 1$ received tapinarof (Vtama) until $\text{PGA} = 0$. Patients with $\text{PGA} = 0$ discontinued tapinarof (Vtama) and were monitored for remittive effect. Patients with $\text{PGA} \geq 2$ were re-treated until $\text{PGA} = 0$. Overall, 91.6% ($n = 763$) of eligible patients enrolled; 40.9% of patients achieved complete disease clearance ($\text{PGA} = 0$), and 58.2% entering with $\text{PGA} \geq 2$ achieved $\text{PGA} = 0$ or 1. Mean duration of off therapy remittive effect for patients achieving $\text{PGA} = 0$ was 130.1 days. No new safety signals were observed.

Atopic Dermatitis

- I. Tapinarof (Vtama) was studied in two identical Phase 3 trials, ADORING 1 and 2. The ADORING trials were both multicenter, randomized, double-blind, vehicle-controlled trials evaluating tapinarof (Vtama) in those two years of age and older with AD. The trials randomized 813 patients 2:1 to tapinarof (vtama) or vehicle cream that was applied once daily for eight weeks. The majority of patients were adolescents (80% between two and 17 years old), with moderate disease on the investigator's global assessment (vIGA-AD) and an average body surface area (BSA) of 16.8%. The primary endpoint was the number of patients achieving treatment success as measured by those reaching clear (0) or almost clear (1) on the vIGA-AD score with at least a 2-grade improvement from baseline.
 - At Week 8, significantly more patients treated with tapinarof (Vtama) than vehicle achieved the primary efficacy endpoint of a vIGA-AD response in both trials: 45.4% in the tapinarof (Vtama) arm compared with 13.9% with vehicle in ADORING 1 ($P < 0.0001$), and 46.4% versus 18.0% in ADORING 2 ($P < 0.0001$)
 - Secondary endpoints showed statistically significant improvements in eczema area and severity index (EASI75) with tapinarof (Vtama) over vehicle, as well as statistically significant improvements in itch response as measured by PP-NRS (peak pruritic-numerical rating scale).

- II. Common treatment emergent adverse events (TEAE) ($\geq 5\%$ in any arm) included folliculitis, headache, and nasopharyngitis. The majority of TEAEs were mild or moderate. Discontinuation rates were lower with tapinarof (VTAMA) compared to the vehicle (ADORING 1: 1.9% vs 3.6%; ADORING 2: 1.5% vs 3.0%).
- The primary and secondary outcomes are validated endpoints that were statistically significant in the ADORING 1 and 2 trials. Tapinarof (VTAMA) demonstrated clinically significant treatment success compared to the vehicle comparator. Additionally, there were minimal safety concerns in the population down to 2 years old.

Investigational or Not Medically Necessary Uses

- I. Tapinarof (Vtama) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
- A. Plaque psoriasis in pediatric or adolescent patients
 - B. Cutaneous Lupus Erythematosus

References

- Lebwohl MG, Stein Gold L, Strober B, et al. Phase 3 trials of tapinarof cream for plaque psoriasis. *N Engl J Med*. 2021;385(24):2219-2229.
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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
Chronic Inflammatory Disease Policy	Plaque psoriasis
Systemic Janus Associated Kinase Inhibitors in Chronic Inflammatory Disease Policy	Plaque psoriasis
dupilumab (Dupixent)	Atopic Dermatitis
lebrikizumab (Ebglyss)	
Systemic Janus Associated Kinase Inhibitors in Chronic Inflammatory Disease Policy	
nemolizumab (Nemluvio)	
ruxolitinib (Jakafi, Opzelura)	
tralokinumab (Adbry)	

Policy Implementation/Update:

Action and Summary of Changes	Date
Removed atopic dermatitis from E/I section and added new indication coverage criteria for atopic dermatitis. Removed the one time allowed quantity limit exception for requests over 60mg/30 days. Revamped supporting evidence section for plaque psoriasis to match current supporting evidence sections.	06/2025
Policy created	08/2022

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP215

Description

Tasimelteon (Hetlio^z, Hetlio^z LQ) is an agonist of melatonin MT1 and MT2 receptors which are thought to be involved in the control of circadian rhythms.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
tasimelteon (Hetlio ^z)	20 mg capsules	Non 24-Hour Sleep-Wake Disorder; Nighttime Sleep Disturbances in Smith-Magenis Syndrome (SMS)	30 capsules/30 days
tasimelteon (Hetlio ^z LQ)	4 mg/mL oral suspension	Nighttime Sleep Disturbances in Smith-Magenis Syndrome (SMS)	0.7 mg/kg*
			158 ml bottle**

* for members weighing 28kg or less

** for members weighing more than 28kg

Initial Evaluation

- I. Tasimelteon (Hetlio^z, Hetlio^z LQ) may be considered medically necessary when the following criteria are met:
 - A. Medication is prescribed by, or in consultation with, a neurologist, sleep specialist, or psychiatrist; **AND**
 - B. Treatment with melatonin (for at least three months continuously) has been ineffective, contraindicated, or not tolerated; **AND**
 - C. A diagnosis of **Non-24-hour sleep-wake disorder (N24HSD)** when the following are met:
 1. Member is 18 years of age or older; **AND**
 2. Member has a diagnosis of total blindness in both eyes without light perception; **AND**
 3. Provider has documented progressively shifting sleep-wake times with sleep diaries and/or actigraphy for at least 14 days; **AND**
 4. Treatment with at least TWO of the following groups has been ineffective or not tolerated, or **all** are contraindicated:
 - i. benzodiazepines (eg. flurazepam, lorazepam, temazepam)
 - ii. non-benzodiazepines (eg. doxepin, eszopiclone, zaleplon)
 - iii. melatonin agonist (eg. ramelteon); **OR**

- D. A diagnosis of **Nighttime sleep disturbances in Smith-Magenis Syndrome (SMS)** when the following are met:
 - 1. Genetic testing has identified a heterozygous deletion of 17p11.2; **OR**
 - i. A heterozygous pathogenic variant involving RAI1; **AND**
 - 2. Request is for tasimelteon (Hetlioz) capsules; **AND**
 - i. Member is 16 years of age or older; **OR**
 - 3. Request is for tasimelteon (Hetlioz LQ) oral solution; **AND**
 - i. Member is between three and 15 years of age; **AND**
 - ii. Current weight provided in documentation
- II. Tasimelteon (Hetlioz, Hetlioz LQ) is considered investigational when used for all other conditions, including but not limited to:
 - A. Sighted individuals with non-24-hour sleep-wake disorder
 - B. Non-24-hour sleep-wake disorder in blind individuals with light perception
 - C. Jet lag disorder
 - D. Major depressive disorder

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Member has exhibited improvement or stability of disease symptoms [e.g. longer duration of nighttime sleep, more alert during the day]

Supporting Evidence

- I. The safety and efficacy of tasimelteon (Hetlioz) has been established in two phase III, placebo-controlled, randomized, double-blind studies (SET and RESET) in totally blind adult patients without light perception in both eyes and with a diagnosis of non-24-hour sleep-wake disorder.
 - Patients were randomized to receive tasimelteon 20mg or placebo every 24 hours at a fixed clock time one hour before target bedtime.
 - Primary outcome measure for the SET study of the proportion of entrained patients assessed in the intention-to-treat population assessed from 6-sulphatoxymelatonin (aMT6s) rhythms for 4 weeks starting from day 14, was met by eight (20%) of 40 patients in the tasimelteon group, compared with one (3%) of 38 patients in the placebo group.
 - Primary outcome measure for the RESET study of the proportion of maintenance of entrainment (aMT6s) has been met by nine (90%) of ten patients in the tasimelteon group, whereas only two (20%) of ten patients withdrawn to placebo, maintained entrainment.

- Entrained is the synchronization or alignment of the internal biological clock rhythm, including its phase and period, to external time cues, such as the natural dark-light cycle.
 - Duration of nighttime sleep was improved by 28 minutes and the duration of daytime napping was reduced by 27 minutes, while each worsened when treatment was withdrawn.
- II. There is a lack of randomized clinical trial data to show safety and efficacy of tasimelteon (Hetlioz) in pediatric patients with the diagnosis of N24SWD. Although the SMS indication is approved in pediatric patients – very few pediatric patients (N=11) have actually received the medication, thus, use for N24HSWD in those under 18 years of age would be considered experimental.
- III. Per the American Academy of Sleep Medicine Clinical Practice Guideline, a diagnosis of N24SWD requires at least 14 days of documentation of progressively shifting sleep-wake times with sleep diaries and/or actigraphy.
- IV. The exogenous melatonin (0.5-10 mg) has been shown to entrain the free-running circadian rhythms of some blind subjects. The American Academy of Sleep Medicine has identified three studies in their guideline. Melatonin was administered either one hour prior to preferred bedtime, or at a fixed clock hour (21:00), for a period of 26–81 days (one to three months). The entrainment rate (12 of 18) found in the current meta-analysis of melatonin treatment in N24SWD was 67%. Due to the lack of head-to-head trials there is no clinical trial data to show that one therapy is superior to the other.
- V. The safety and efficacy of tasimelteon (Hetlioz) for Nighttime Sleep Disturbances in SMS has been established a pivotal phase 2/3, nine-week, double-blind, randomized, placebo-controlled, two-period crossover study in 14 adults and 11 pediatric patients.
- Patients 16 years of age and older received 20 mg capsules, and pediatric patients three years to 15 years of age received a weight-based dose of oral suspension.
 - The primary endpoints in were nighttime total sleep time [assessed via daily diary total nighttime sleep duration (DDTST)] and nighttime sleep quality from a parent/guardian-recorded diary (DDSQ). The efficacy comparisons for nighttime sleep quality and total sleep time were based on the 50% of nights with the worst sleep quality and the 50% of nights with the least nighttime sleep in each 4-week period.
 - Compared to placebo, treatment with tasimelteon (Hetlioz) resulted in a statistically significant improvement in the 50% worst nights' sleep quality. Although improvement on the 50% worst total nighttime sleep time numerically favored tasimelteon (Hetlioz) treatment, the difference was not statistically significant.

Primary Efficacy Measures	Treatment Group	LS Meana (SE)	Placebo-subtracted Difference (95% CI)
Average of 50% Worst Daily Nighttime Sleep Quality*	HETLIOZ (n=25)	2.8 (0.15)	0.4 (0.1, 0.7)
	Placebo (n=25)	2.4 (0.15)	-
Average of 50% Worst Daily	HETLIOZ (n=25)	7.0 (0.26)	0.3 (-0.0, 0.6)
	Placebo (n=25)	6.7 (0.26) -	-

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Nighttime Total Sleep Time, hours			

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval unadjusted for multiplicity.

^a LS Means are the model-based averages based on the 50% worst days per 4-week period.

^b Difference (drug minus placebo) in least-squares means.

* Endpoint on which HETLIOZ was statistically significant different from placebo after controlling for multiple comparisons.

- VI. The recommended dosage of tasimelteon (Hetlioz LQ) oral suspension for the treatment of nighttime sleep disturbance in SMS pediatric patients three to 15 years of age is by body weight. For patients with 28 kg or less the recommended dose is 0.7 mg/kg and for patients who weigh more than 28kg the recommended dose is 20 mg one hour before bedtime.
- VII. Smith-Magenis syndrome (SMS) is a developmental disorder that affects many parts of the body. The major features of this condition include mild to moderate intellectual disability, delayed speech and language skills, distinctive facial features, sleep disturbances, and behavioral problems. Most people with SMS have a deletion of genetic material in each cell from a specific region of chromosome 17. Although this region contains multiple genes, researchers believe that the loss of one particular gene, RAI1, is responsible for most of the features of the condition. In most of these cases, the deletion is not inherited, occurring randomly during the formation of eggs or sperm, or in early fetal development.
 - The diagnosis of SMS is established in a proband with suggestive clinical features and one of the following on molecular genetic testing: A heterozygous deletion of 17p11.2 or heterozygous pathogenic variant involving RAI1. When the phenotypic findings suggest the diagnosis of SMS, molecular genetic testing approaches can include chromosomal microarray analysis, single-gene testing, or use of a multigene panel.
- VIII. Recent studies have attributed the sleep disturbance in SMS to a primary disturbance of the circadian clock, with RAI1 functioning as a positive regulator of Circadian Locomotor Output Cycles Kaput (CLOCK) transcription, a key component of the mammalian circadian oscillator. Additionally, disrupted melatonin secretion has been noted with moderate to high levels of daytime salivary melatonin observed in SMS patients.
- IX. As patients with SMS typically display a diurnal rather than nocturnal peak in melatonin secretion, exogenous melatonin has been used nocturnally to supplement the typical biological melatonin secretion. By adding an exogenous melatonin dose prior to bedtime, a nocturnal rise in melatonin levels can assist in increasing the biological propensity to sleep. Given the very limited experience of tasimelteon (Hetlioz) in pediatric populations, the safety and efficacy profile are largely unknown. Melatonin has a more established safety and efficacy profile and should be considered for use prior to tasimelteon (Hetlioz).

Investigational or Not Medically Necessary Uses

- I. Tasimelteon (Hetlioz) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Sighted individuals with non-24-hour sleep-wake disorder and non-24-hour sleep-wake disorder in blind individuals with light perception
 - i. There no published clinical trial data to show safety and efficacy and support the use of tasimelteon (Hetlioz) in these patient populations.
 - B. Jet lag disorder

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- i. A phase II, randomized, double blind proof of concept study to evaluate the effects of tasimelteon and placebo in travelers with jet lag disorder with the primary outcome measure of changes in sleep after transmeridian travel measured by nighttime sleep parameters
 - ii. A randomized, double-blind, placebo-controlled, parallel design study evaluating the effects of tasimelteon compared to placebo on jet lag type insomnia enrolled 320 healthy adult patients. Tasimelteon treatment increased Total Sleep Time in the first 2/3 of the night (primary endpoint) by 60.3 min (95%CI 44.0 to 76.7, $P < 0.0001$) and whole night TST by 85.5 min (95% CI 64.3 to 106.6, $P < 0.0001$), improved next day alertness, next day sleepiness, and shortened latency to persistent sleep by -15.1 min (95% CI -26.2 to -4.0, $P = 0.0081$).
 - iii. Jet Lag was induced by an immediate phase advance of the sleep-wake cycle in a sleep clinic, rather than jet travel in the eastward direction.
 - iv. There isn't robust safety and efficacy data to support the use of tasimelteon (Hetlioz) in the treatment of the jet lag disorder.
- C. Major Depressive Disorder (MDD)
- i. A randomized, parallel, double-masked, placebo-controlled, multicenter outpatient study comparing tasimelteon with placebo with 507 enrolled participants (MAGELLAN) followed by a 52-week open label extension.
 - o The primary outcome measure was change from baseline to endpoint at week 8 using the total score of Hamilton Depression Rating Scale (HAM-D) was not met.
 - o The clinical trial showed insufficient efficacy and limited safety data.

References

1. Hetlioz [Prescribing Information]. Washington, D.C. Vanda Pharmaceuticals Inc. October 2019.
2. Lockley SW, et al. Tasimelteon for non-24-hour sleep-wake disorder in totally blind people (SET and RESET): two multicentre, randomised, double-masked, placebo-controlled phase 3 trials. *Lancet*. 2015;386(10005):1754-1764. doi:10.1016/S0140-6736(15)60031-9
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6. Vanda Pharmaceuticals. Melatonin Agonist Effects of Tasimelteon Versus Placebo in Patients With Major Depressive Disorder (MAGELLAN). ClinicalTrials.gov Identifier: NCT01428661
7. Brian J. Shayota, et al. Behavior and Sleep Disturbance in Smith-Magenis Syndrome. *Curr Opin Psychiatry*. 2019 Mar; 32(2): 73–78. doi: 10.1097/YCO.000000000000047
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9. Vanda Pharmaceuticals. A Proof of Concept Study to Evaluate the Effects of Tasimelteon and Placebo in Travelers With Jet Lag Disorder. ClinicalTrials.gov Identifier: NCT03291041

10. Polymeropoulos CM, Mohrman MA, Keefe MS, et al. Efficacy of Tasimelteon (HETLIOZ®) in the Treatment of Jet Lag Disorder Evaluated in an 8-h Phase Advance Model; a Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial. *Front Neurol.* 2020;11:611. Published 2020 Jul 9. doi:10.3389/fneur.2020.00611
11. Vanda Pharmaceuticals. Melatonin Agonist Effects of Tasimelteon Versus Placebo in Patients With Major Depressive Disorder (MAGELLAN). *ClinicalTrials.gov* Identifier: NCT01428661
12. NIH Genetics and Rare Diseases (GARD). Smith-Magenis syndrome. <https://rarediseases.info.nih.gov/diseases/8197/smith-magenis-syndrome>
13. Smith ACM, Boyd KE, Elsea SH, et. al. Smith-Magenis Syndrome. *GeneReviews*. June 28, 2012; <https://www.ncbi.nlm.nih.gov/books/NBK1310/>.
14. Smith Magenis Syndrome. *NORD*. 2017; <https://rarediseases.org/rare-diseases/smith-magenis-syndrome/>.

Policy Implementation/Update:

Action and Summary of Changes	Date
- Added new indication of Nighttime Sleep Disturbances in SMS - Added a new formulation, the tasimelteon (Hetlio LQ) oral solution - New criteria added for the indication of N24HSWD: - Treatment with melatonin (for at least three months continuously) has been ineffective, contraindicated or not tolerated - Member has a diagnosis of total blindness in both eyes without light perception - Provider has documented progressively shifting sleep-wake times with sleep diaries and/or actigraphy for at least 14 days - Treatment with at least TWO alternatives has been ineffective or not tolerated, or all are contraindicated: benzodiazepines (eg. flurazepam, lorazepam, temazepam), or non-benzodiazepines (eg. doxepin, eszopiclone, zaleplon) or melatonin agonist (eg. ramelteon) - Criteria removed from the indication of N24HSWD: - Member has no hepatic impairment or mild to moderate hepatic impairment - Member is not on concurrent strong CYP3A4 inducers or CYP1A2 inhibitors Criteria updated to policy format	12/2020
Criteria created	04/2014

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP024

Description

Teduglutide (Gattex) is a subcutaneously administered recombinant synthetic glucagon like peptide 2 (GLP-2) analog.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit	DDID
teduglutide (Gattex)	5 mg vial kit (one vial)	Short Bowel Syndrome (SBS)	1 vial/1 day	177513
	5 mg vial kit (30 vial)		30 vials/30 days	

Initial Evaluation

- I. Teduglutide (Gattex) may be considered medically necessary when the following criteria below are met:
 - A. Member is one year of age or older and weighs more than 10 kg; **AND**
 - B. Teduglutide (Gattex) has been prescribed by, or consultation with a specialist in gastroenterology; **AND**
 - C. A diagnosis of **Short Bowel Syndrome**; **AND**
 1. Member dependence on parenteral nutrition/intravenous support for at least 12 months; **AND**
 2. Member dependence on parenteral nutrition at least three times a week; **AND**
 3. Laboratory assessment within the last six months of bilirubin, alkaline phosphatase, lipase and amylase to rule out gallbladder, biliary tract or pancreatic disease; **AND**
 4. Colonoscopy within the last 6 months to rule out colorectal polyps or small bowel neoplasia in adult members; **OR**
 5. Fecal occult blood testing in children and adolescents within the last 6 months; **AND**
 - i. Documentation of a follow-up colonoscopy for any positive fecal occult blood test
- II. Teduglutide (Gattex) is considered investigational when used for all other conditions, including but not limited to:

- A. Crohn's disease
- B. Enterocutaneous Fistula (ECF)
- C. Gastric emptying

Renewal Evaluation

- I. Clinical documentation of response to therapy as demonstrated by:
 - A. Decrease in volume of parenteral or intravenous nutritional support; **OR**
 - B. Decrease in number of days of parenteral or intravenous nutritional support; **AND**
- II. Colonoscopy performed within the last 12 months to rule out colorectal polyps or small bowel neoplasia upon first renewal, and, no less than every five years; **AND**
- III. Bilirubin, alkaline phosphatase, lipase, and amylase laboratory assessment to rule out gallbladder, biliary tract or pancreatic disease within the last six months.

Supporting Evidence

- I. Teduglutide (Gattex) is FDA approved for treatment adults and pediatric patients 1 year of age or older with Short Bowel Syndrome (SBS) who are dependent on parenteral support.
- II. The pivotal trial included patients with SBS who were dependent on parenteral nutrition/intravenous support for at least 12 months and at least 3 times per week.
- III. There is a lack of strong scientific evidence from randomized controlled trials supporting safety and efficacy for an increased dosing frequency. The higher dose treatment arm did not demonstrate a statistically significant difference when compared to placebo.
- IV. Colonoscopies should be completed again 1 year after treatment then no less frequently than every 5 years to evaluate for polyps and gastrointestinal malignancies.
- V. Lab assessments are recommended every 6 months to evaluate for gallbladder, biliary tract and pancreatic disease.

Investigational or Not Medically Necessary Uses

- I. Crohn's Disease
 - A. Phase II clinical trials have evaluated teduglutide for the treatment of Crohn's disease.
 - B. Clinical concerns for the safety of teduglutide in patients with Crohn's disease include neoplastic growth, intestinal obstruction and biliary and pancreatic disease.
 - C. Large, well-controlled clinical trials are needed to demonstrate benefit of use of teduglutide in patients with Crohn's Disease.
- II. Clinical trials are ongoing in the following indications:
 - A. Enterocutaneous Fistula (ECF)
 - B. Gastric emptying

References

1. Gattex [Prescribing Information]. Bedminister, NJ: NPS Pharmaceutical; June 2019.
2. Jeppesen PB, Gilroy R, Pertkiewicz M, Allard JP, Messing B, O'Keefe SJ. Randomized placebo-controlled trial of teduglutide in reducing parenteral nutrition and/or intravenous fluid requirements in patients with short bowel syndrome. Gut. 2011 Jul;60(7):902-14

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Policy Implementation/Update:

Date Created	May 2013
Date Effective	May 2013
Last Updated	August 2013
Last Reviewed	05/2013, 09/2013, 06/2019

Action and Summary of Changes	Date
Created new policy format. Addition of new FDA approved indication in pediatric population.	06/2019

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP087

Description

Tegaserod (Zelnorm) is an orally administered serotonin-4 (5-HT₄) receptor agonist.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
tegaserod (Zelnorm)	6 mg tablets	Irritable bowel syndrome with constipation	60 tablets/30 days

Initial Evaluation

- I. Tegaserod (Zelnorm) may be considered medically necessary when the following criteria below are met:
 - A. The member is between 18 and 65 years of age; **AND**
 - B. The medication is prescribed by, or in consultation with, a gastroenterologist; **AND**
 - C. A diagnosis of **irritable bowel syndrome with constipation (IBS-C)** when the following are met:
 1. The member is female; **AND**
 2. The member does not have current, or historical, cardiovascular disease; **AND**
 3. The member has had an inadequate response to the ALL of the following, unless all are contraindicated:
 - i. Dietary modifications (e.g., removal of offending foods, increased fiber intake) **AND** increased physical activity; **AND**
 - ii. At least one osmotic laxative (e.g., polyethylene glycol); **AND**
 - iii. Plecanatide (Trulance); **AND**
 - iv. Linaclotide (Linzess); **AND**
 - v. Lubiprostone (Amitiza)
- II. Tegaserod (Zelnorm) is considered not medically necessary when criteria above are not met and/or when used for:
 - A. Irritable bowel syndrome with constipation in males
- III. Tegaserod (Zelnorm) is considered investigational when used for all other conditions, including but not limited to:
 - A. Idiopathic chronic constipation

- B. Opioid or other drug induced constipation
- C. Gastroesophageal reflux disease (GERD)

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. The member is between 18 and 65 years of age; **AND**
- IV. The medication is prescribed by, or in consultation with, a gastroenterologist; **AND**
 - A. **A diagnosis of irritable bowel syndrome with constipation (IBS-C); AND**
 - 1. The member does not have a history of, or current cardiovascular disease; **AND**
 - 2. The member has experienced a response to treatment (e.g. increase in rate of bowel movements)

Supporting Evidence

- I. Tegaserod (Zelnorm), a serotonin-4 (5-HT₄) receptor agonist, is FDA-approved and indicated for the treatment of irritable bowel syndrome with constipation (IBS-C) in women < 65 years of age. It was originally approved in 2002, for short-term treatment of women with IBS-C; however, it was withdrawn from the market in 2007 due to an unfavorable cardiovascular (CV) and suicidal ideation and behavior (SI/B) safety profile.
- II. Efficacy to support reintroduction of tegaserod (Zelnorm) was based on evidence established at the time of original approval and no new evidence on efficacy has been added. Tegaserod (Zelnorm) was evaluated in three multicenter, double-blind, placebo-controlled, 12-week trials of 2,470 women that had at least a three-month history of IBS-C. Response rate (RR) was the primary outcome, and was based on subjective response on a five parameter scale measured each week indicating: completely relieved, considerably relieved, somewhat relieved, unchanged, or worse. Tegaserod (Zelnorm) had superior response rates compared to placebo ranging from 6 to 28%. Secondary outcomes of pain, discomfort and bloating were evaluated on a six-to-seven-point intensity scale. Positive response, defined as at least a 1-point reduction, was measured to be 1-10% superior for tegaserod (Zelnorm) for abdominal pain or discomfort and 4-11% for bloating. The baseline bowel movement rate averaged 3.8 per week and increased to 6 per week for tegaserod (Zelnorm) and 5.5 for placebo.
- III. During clinical trials, responders were defined as participants with complete relief or considerable relief for at least two of the four weeks, or somewhat relieved for all of the four weeks (after one month of treatment). It is recommended to assess response to treatment after four to six weeks of treatment, and to discontinue tegaserod (Zelnorm) for nonresponsive patients.
- IV. Tegaserod (Zelnorm) is contraindicated in those with established CV history (specifically, myocardial infarction, stroke, transient ischemic attack, angina), renal impairment, hepatic impairment, bowel obstruction, gallbladder disease, suspected sphincter of Oddi dysfunction, or

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abdominal adhesions. Warnings and precautions include CV ischemic events, major adverse CV events (MACE), ischemic colitis, volume depletion with diarrhea, and SI/B. Common adverse effects ($\geq 2\%$) include headache, abdominal pain, nausea, diarrhea, flatulence, dyspepsia, and dizziness. Approval of tegaserod (Zelnorm) reintroduction was supported by a complete safety review by the FDA and FDA-assembled Gastrointestinal Drugs Advisory Committee (GIDAC). Retrospective analyses of pooled data from 18,645 patients in 29 placebo-controlled trials in various disease states of at least four weeks duration were included. The imbalance in CV events was measured to be 0.1% for tegaserod (Zelnorm) versus 0.01% in placebo. There was one death, attributed to suicide, during the trial; although, the member had a history of mild depression. The rate of SI/B is measured to be 0.07% for tegaserod (Zelnorm) vs. 0.02% for placebo.

- V. First-line treatment options for the treatment of IBS-C include dietary modifications, increased fiber intake, and physical activity. Adjunctive pharmacotherapy includes over-the-counter osmotic laxatives. When lifestyle modifications and osmotic laxatives fail to produce sufficient relief of constipation, further pharmacological interventions are indicated. The 2021 American College of Gastroenterology (ACG) clinical guidelines for management of IBS recommend use of guanylate cyclase activators (e.g. linaclotide [Linzess], plecanatide [Trulance]) and chloride channel activator (e.g. lubiprostone [Amitiza]) as recommended therapeutic options based on high and moderate quality of clinical evidence, respectively. Tegaserod (Zelnorm) may be considered a subsequent-line therapy based on a conditional recommendation (low quality of evidence) from ACG review panel. Thus, due to the limited efficacy and concerning safety profile, tegaserod (Zelnorm) should only be reserved for those that have exhausted other treatment options.

Investigational or Not Medically Necessary Uses

- I. Irritable bowel syndrome with constipation (IBS-C) in males
 - A. Two randomized, placebo-controlled, double-blind trials of 288 men did not show differences in efficacy of tegaserod (Zelnorm) versus placebo. This information is stated in the product labeling.
- II. Clinical trials are underway, but have not yet been completed to provide insight to safety and efficacy of tegaserod (Zelnorm) in the following settings:
 - A. Idiopathic chronic constipation
 - B. Opioid or other drug induced constipation
 - C. Gastroesophageal reflux disease (GERD)

References

1. Zelnorm [Prescribing Information]. Sloan Pharma/WorldMeds LLC. Louisville, KY. 2019.
2. Black CJ, Burr NE, Ford AC. Relative Efficacy of Tegaserod in a Systematic Review and Network Meta-analysis of Licensed Therapies for Irritable Bowel Syndrome with Constipation. Clin Gastroenterol Hepatol. 2019.
3. Vakil N, Laine L, Talley NJ, et al. Tegaserod treatment for dysmotility-like functional dyspepsia: results of two randomized, controlled trials. Am J Gastroenterol. 2008;103(8):1906-19.
4. Weinberg D.S., Smalley W. Heidelbaugh J.J., et al. American Gastroenterological Association institute guidelines on the pharmacological management of irritable bowel syndrome. Gastroenterology. 2014;144: 1146-1148.
5. Chandar AK. Diagnosis and treatment of irritable bowel syndrome with predominant constipation in the primary-care setting: focus on linaclotide. Int J Gen Med. 2017;10:385-393.

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6. FDA Joint Meeting of the Gastrointestinal Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee Briefing Document; Sloan Pharma; US WorldMeds, 10/17/2018; accessed via <https://www.fda.gov/media/119013/download>
7. Lacy BE, Pimentel M, Brenner DM, Chey WD, Keefer LA, Long MD, Moshiree B. ACG Clinical Guideline: Management of Irritable Bowel Syndrome. Am J Gastroenterol. 2021 Jan 1;116(1):17-44.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy updated to require trials of Trulance, Linzess, AND Amitiza for coverage consideration of Zelnorm; updated supporting evidence to reflect 2021 ACG guideline recommendations; made minor formatting changes to align policy with current format; (Effective 7/1/2021)	05/2021
Policy created	08/2019

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP155

Description

Telotristat ethyl (Xermelo) is an orally administered tryptophan hydroxylase inhibitor indicated for the treatment of carcinoid syndrome diarrhea in combination with somatostatin analog (SSA) therapy in adults inadequately controlled by SSA therapy.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
telotristat ethyl (Xermelo)	250 mg tablets	Carcinoid Syndrome Diarrhea	84 tablets/28 days

Initial Evaluation

- I. Telotristat ethyl (Xermelo) may be considered medically necessary when the following criteria below are met:
 - A. Member is 18 years of age or older; **AND**
 - B. Medication is prescribed by, or in consultation with, oncologist or gastroenterologist; **AND**
 - C. Telotristat ethyl (Xermelo) will be used in combination with a somatostatin analog therapy (e.g., octreotide [Sandostatin/Sandostatin LAR depot], lareotide [Somatuline depot]); **AND**
 - D. A diagnosis of **carcinoid syndrome diarrhea** when the following are met:
 1. Clinical documentation of significant diarrhea (≥ 4 bowel movements per day on average); **AND**
 2. Treatment with a somatostatin analog therapy (e.g. octreotide [Sandostatin/Sandostatin LAR depot], lareotide [Somatuline depot]) has not been effective after at least 3 months of therapy, was not tolerated, or is contraindicated.
- II. Telotristat ethyl (Xermelo) is considered investigational when used for all other conditions, including but not limited to:
 - A. Carcinoid syndrome without diarrhea
 - B. Biliary Tract Cancer
 - C. Pancreatic Cancer

Renewal Evaluation

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- I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Member has exhibited improvement or stability of disease symptoms defined by a decrease in overall average bowel movements per week from baseline; **AND**
- IV. Telotristat ethyl (Xermelo) will be used in combination with a somatostatin analog therapy (e.g., octreotide [Sandostatin/Sandostatin LAR depot], lareotide [Somatuline depot]).

Supporting Evidence

- I. The safety and efficacy for telotristat ethyl (Xermelo) was studied in a 12-week double-blind, placebo-controlled, randomized, multicenter trial in adult patients with well differentiated metastatic neuroendocrine tumor and carcinoid syndrome diarrhea who were having between 4 to 12 daily bowel movements despite the use of SSA therapy at a stable dose for at least 3 months. The primary efficacy outcome was the change from baseline in the number of daily bowel movements averaged over the 12-week treatment period; in the telotristat ethyl (Xermelo) arm, there was a reduction of -1.4 bowel movements per day compared to -0.6 in the placebo arm with $p < 0.001$.

Investigational or Not Medically Necessary Uses

- I. There is a lack of strong scientific evidence from randomized controlled trials supporting safety and efficacy for the following indications:
 - A. Carcinoid syndrome without diarrhea
 - B. Biliary Tract Cancer
 - C. Pancreatic Cancer/Other Neuroendocrine Tumors (NETs)

References

1. Xermelo [Prescribing Information]. Woodlands, TX: Lexicon Pharmaceuticals, Inc. February 2017.
2. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN guidelines®): Neuroendocrine Tumors of the Gastrointestinal Tract, Lung, and Thymus (Carcinoid Tumors). Version 1.2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine_blocks.pdf

Policy Implementation/Update:

Date Created	11/2019
Date Effective	December 2019
Last Updated	
Last Reviewed	

Action and Summary of Changes	Date

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP163

Description

Temozolomide is an alkylating agent that undergoes rapid nonenzymatic conversion to the reactive compound 5-(3-methyltriazen-1-yl) imidazole-4-carboxamide (MTIC). The cytotoxicity of MTIC is thought to be caused primarily by alkylation of DNA. Alkylation (methylation) occurs mainly at the O⁶ and N⁷ positions of guanine which leads to DNA double strand breaks and apoptosis.

Length of Authorization

- Initial: Three months
- Renewal: Six months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
temozolomide (Temodar)	5 mg capsules	All indications	Maximum 200 mg/m ² /day
	20 mg capsules		
	100 mg capsules		
	140 mg capsules		
	180 mg capsules		
	250 mg capsules		
Provider Administered Agents*			
temozolomide (Temodar)	100 mg vial	All indications	Maximum 200 mg/m ² /day

**Medical drug that requires administration by a healthcare professional and is not available for self-administration by the member, considered one of the excluded classes under the prescription benefit.*

Initial Evaluation

- Temozolomide (Temodar) may be considered medically necessary when treatment with generic temozolomide has been ineffective, contraindicated, or not tolerated.

Renewal Evaluation

- Member has received a previous prior authorization approval for this agent through this health plan; **AND**
- Disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread.

References

1. Temodar (temozolomide) [Prescribing Information]. Whitehouse Station, NJ: Merck & Co. October 2017.

Policy Implementation/Update:

Action and Summary of Changes	Date
- Removed generic temozolomide from the policy - Removed indication-specific criteria	03/2020
Updated to policy format	12/2019
Previous reviews	03/2016
Policy created	05/2012

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP170

Description

Tenapanor (e.g., Ibsrela, Xphozah) is an orally administered sodium/hydrogen exchange 3 (NHE3) inhibitor.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
tenapanor (Ibsrela)	Irritable bowel syndrome with constipation (IBS-C)	50 mg tablets	60 tablets/30 days
tenapanor (Xphozah)	Reduction of serum phosphorus in adults with chronic kidney disease (CKD) on dialysis as add-on therapy in patients who have an inadequate response to phosphate binders or who are intolerant of any dose of phosphate binder therapy	10 mg tablets	60 tablets/30 days
		20 mg tablets	
		30 mg tablets	

Irritable bowel syndrome with constipation (IBS-C)

Initial Evaluation

- I. **Tenapanor (Ibsrela)** may be considered medically necessary when the following criteria below are met:
 - A. The member is 18 years of age or older; **AND**
 - B. The medication is prescribed by, or in consultation with, a gastroenterologist; **AND**
 - C. A diagnosis of **irritable bowel syndrome with constipation (IBS-C)** when the following are met:
 1. The member has had an inadequate response, or intolerance to, all of the following, unless all are contraindicated (*Please note: These agents may be subject to additional prior authorization review):
 - i. Dietary and lifestyle modifications (e.g., removal of offending foods, increased fiber intake) and increased physical activity; **AND**
 - ii. At least one osmotic laxative (e.g., polyethylene glycol); **AND**
 - iii. Plecanatide (Trulance); **AND**
 - iv. Lubiprostone or Amitiza*; **AND**
 - v. Linaclotide (Linzess)*

- II. Tenapanor (Ibsrela) is considered investigational when used for all other conditions, including but not limited to:
 - A. Hyperphosphatemia
 - B. Chronic kidney disease
 - C. Irritable bowel syndrome with diarrhea
 - D. Mixed irritable bowel syndrome
 - E. Chronic idiopathic constipation
 - F. Opioid-induced constipation

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Member has a diagnosis of irritable bowel syndrome with constipation (IBS-C); **AND**
- IV. Member has exhibited improvement or stability of disease symptoms (e.g., improvement in complete spontaneous bowel movements per week from baseline, reduction in abdominal pain)

Supporting Evidence

- I. Tenapanor (Ibsrela) is approved by the US Food and Drug Administration (US-FDA) for the treatment of irritable bowel syndrome with constipation (IBS-C) in adults.
- II. Given the complexities involved in diagnosis and management of IBS-C, as well as required monitoring for adverse events and therapy response, therapy decisions regarding initiation of tenapanor (Ibsrela) must be made by, or under the supervision of, a specialist practicing in this setting (e.g., gastroenterologist).
- III. Tenapanor (Ibsrela) is a sodium/hydrogen exchange 3 (NHE3) inhibitor acting specifically in the GI tract, with minimal systemic availability following oral administration. Inhibition of NHE3 leads to a reduction in dietary sodium absorption and an increase in intracellular protons across membranes in the GI tract, which results in reduction of phosphate absorption from the small intestine and colon. Additionally, consequent increase in sodium and phosphorus content in the stool, decreased urinary sodium and phosphorus excretion, and increased water secretion into the intestinal lumen and the increased stool water content leads to loosened stool consistency and increased bowel movement frequency.
- IV. Tenapanor (Ibsrela) has a Black Box Warning for serious dehydration in pediatric patients and has not been evaluated in any pediatric population to date. It is contraindicated in those less than six years of age and comes with a recommendation to avoid use in those less than 12 years of age due to animal studies showing cause of death to be dehydration in young juvenile rats. Additionally, tenapanor (Ibsrela) is also contraindicated in patients with known or suspected mechanical gastrointestinal obstruction.
- V. **Irritable Bowel Syndrome with Constipation (IBS-C):** Tenapanor (Ibsrela) was evaluated in two double-blind, placebo-controlled, randomized trials in adult patients –T3MPO-2 and T3MPO-1. The majority of subjects were female (83%), white, and all met Rome III criteria for IBS-C. This

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requires a pain score of at least three on a 0-10 scale, less than three complete spontaneous bowel movements (CSBMs) per week, and less than five spontaneous bowel movements (SBMs) per week.

- The primary outcome was proportion of responders, defined as achieving both of the following for at least six of the first 12 weeks of the trials: an increase of at least one CSBM per week on average and a reduction of 30% in weekly average abdominal pain score compared to baseline.
- T3MPO-2: 620 subjects were evaluated for 26 weeks of treatment. Responders active vs. placebo: 37% vs. 24% (CI 6-20%). Difference from placebo 13%.
- T3MPO-1: 606 subjects were evaluated for 12 weeks and then were re-randomized to active drug or placebo for a 4-week withdrawal period. Responders active vs. placebo: 27% vs. 19% (CI: 2-15%). Difference from placebo 8%.

- VI. The quality of the evidence is considered low given the invalidated subjective endpoints used to determine efficacy and the short duration of therapy evaluated for safety and efficacy.
- VII. First-line treatment options for the treatment of IBS-C include dietary modifications, increased fiber intake, and physical activity. Adjunctive pharmacotherapy includes over-the-counter osmotic laxatives. When lifestyle modifications and osmotic laxatives fail to produce sufficient relief of constipation, further pharmacological interventions are indicated. The 2021 American College of Gastroenterology (ACG) clinical guidelines for management of IBS-C recommend use of guanylate cyclase activators (e.g., linaclotide [Linzess], plecanatide [Trulance]) and chloride channel activator (e.g., lubiprostone [Amitiza]) as recommended therapeutic options based on high and moderate quality of clinical evidence, respectively. As of March 2022, the ACG guidelines do not include tenapanor (Ibsrela) as a recommended agent for the treatment of IBS-C. Based on the clinical evidence showing limited treatment effect and lack of place in therapy information, usability of tenapanor (Ibsrela) is uncertain at this time. Thus, use of non-pharmacologic agents and other established therapies are warranted prior to payment consideration for tenapanor (Ibsrela).

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Hyperphosphatemia in Chronic Kidney Disease (CKD)

Initial Evaluation

- I. **Tenapanor (Xphozah)** may be considered medically necessary when the following criteria below are met:
 - A. Member is 18 years of age or older; **AND**
 - B. The medication is prescribed by, or in consultation with, a nephrologist; **AND**
 - C. A diagnosis of **hyperphosphatemia in Chronic Kidney Disease (CKD)**; **AND**
 1. Member is currently receiving and has been stable on maintenance hemodialysis or peritoneal dialysis for 3 months; **AND**
 2. Presence of hyperphosphatemia, defined as serum phosphate levels >5.5mg/dL within the past 3 months; **AND**
 3. Provider attestation that hyperphosphatemia is not due to a reversible/untreated secondary cause (e.g., hypoparathyroidism, high phosphate containing medications/formulations); **AND**
 - D. The member has had an inadequate response, contraindication, or intolerance to, all of the following:
 1. Dietary and lifestyle modifications (e.g., low phosphorus diet); **AND**
 2. Three of the following phosphate binders:
 - i. Sevelamer hydrochloride or sevelamer carbonate*
 - ii. Lanthanum carbonate*
 - iii. Sucroferric oxyhydroxide (Velphoro)*
 - iv. Ferric Citrate (Auryxia)*
- II. Tenapanor (Xphozah) is considered investigational when used for all other conditions, including but not limited to:
 - A. Non-dialysis dependent hyperphosphatemia in chronic kidney disease
 - B. Irritable bowel syndrome with diarrhea
 - C. Mixed irritable bowel syndrome
 - D. Chronic idiopathic constipation
 - E. Opioid-induced constipation

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Member has a diagnosis of hyperphosphatemia in chronic kidney disease (CKD); **AND**
- IV. Member is currently receiving and has been stable on maintenance hemodialysis or peritoneal dialysis for 3 months; **AND**

- V. Member has exhibited improvement or stability of disease symptoms (e.g., reduction of serum phosphate from baseline or maintenance of serum phosphorus levels within normal range <5.5mg/dL)

Supporting Evidence

- I. Excess serum phosphate levels promote vascular calcification and induces endothelial dysfunction leading to cardiovascular toxicity and disease. If left untreated, hyperphosphatemia is correlated with vascular and tissue calcifications, bone pain/fractures, and worsening secondary hyperparathyroidism.
- II. The diagnosis and management of chronic kidney disease (CKD) in patients on dialysis requires detailed clinical examination, frequent monitoring of labs, and highly individualized treatment regimens. Given the complexities of treatment of hyperphosphatemia in this patient population, supervision or consultation with a nephrologist is required.
- III. CKD is defined as abnormalities of kidney structure or function present for greater than 3 months. Estimated Glomerular filtration rate (eGFR) category (G1-G5) is used to categorize CKD. An eGFR ≥ 90 mL/min/1.73m² (G1) is normal or high, eGFR between 60-89 mL/min/1.73m² (G2) is considered mildly decreased, 45-59 mL/min/1.73m² (G3a) is mildly to moderately decreased, 30-44 mL/min/1.73m² (G3b) is moderately to severely decreased, 15-29 mL/min/1.73m² (G4) is severely decreased, and <15 mL/min/1.73m² (G5) or requiring dialysis is considered kidney failure. Within clinical guidelines, recommendations for treatment of hyperphosphatemia applies to patients in categories G3a-G5d (i.e., GFR <60 mL/min).
- IV. Tenapanor (Xphozah) was studied in patients with CKD requiring dialysis, therefore, the safety, efficacy, and utility of tenapanor (Xphozah) in patients without CKD or in those not requiring dialysis has not been established. Patients with CKD requiring dialysis are at greater risk of developing hyperphosphatemia and at higher risk of CKD related morbidity and mortality. Within all Phase III clinical trials, patients were required to be on chronic maintenance hemodialysis for at least 3 months prior to study enrollment.
- V. The safety and efficacy of tenapanor (Xphozah) was evaluated in three Phase III trials (AMPLIFY, PHREEDOM, ESRD-HD), and one Phase IV open-label extension trial (NORMALIZE).
 - AMPLIFY was a Phase III, double-blind, multicenter, placebo-controlled trial enrolling 236 patients undergoing maintenance dialysis with hyperphosphatemia despite receiving phosphate binder therapy (including sevelamer, non-sevelamer, sevelamer plus non-sevelamer, or multiple non-sevelamer binders). Patients were randomized to receive oral tenapanor (Xphozah) 30 mg twice daily plus phosphate binder or placebo plus phosphate binder for 4 weeks. The primary efficacy endpoint was change in serum phosphorus concentration from baseline to week 4, and key secondary endpoints were proportion of patients with serum phosphorus levels < 5.5mg/dL at weeks 1-4. At week 4, patients receiving tenapanor (Xphozah) plus phosphate binder had a significantly larger least squares mean change in serum phosphorus concentration from baseline when compared to placebo plus phosphate binder (-0.84 vs -0.19 mg/dL, p<0.001). At week 1, 49.1% of patients in the tenapanor (Xphozah) + binder arm achieved serum phosphorus <5.5 mg/dL versus 21.0% of patients for the placebo + binder arm (p<0.001). This effect was sustained through week 2 (41.4% vs 23.5%, p=0.003), week 3 (47.3% vs 17.6%, p<0.001), and week 4 (37.1% vs 21.8%, p=0.01), respectively.
 - PHREEDOM was a 564 patient, 52-week, Phase III, multicenter trial consisting of three parts, a 26-week open-label randomized treatment period (RTP), a 12-week

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double-blind placebo-controlled randomized withdrawal period (RWP), and a 14-week open-label safety extension period (SEP). After a washout period, patients were randomized 3:1 to either tenapanor (Xphozah) for 26 weeks or sevelamer for 52 weeks. Patients in the tenapanor (Xphozah) arm were randomized into a withdrawal period to be continued on tenapanor (Xphozah) or placebo for 12 weeks, followed by an optional 14-week safety extension period. The primary end point was the change in serum phosphorous from the end of the RTP to the end of the RWP, among participants who achieved ≥ 1.2 mg/dl decrease in serum phosphate during the RTP (efficacy analysis set). In the ITT population, there was a mean difference of 1.4 mg/dL between baseline phosphate and phosphate at 26 weeks for the tenapanor (Xphozah) arm during the 26-week RTP, and a -0.66 mg/dL difference between tenapanor (Xphozah) and placebo in the 12-week RWP ($p=0.002$). During the RTP, 53% of patients who received tenapanor (Xphozah) experienced diarrhea as an adverse event vs 7% for sevelamer. Twenty four percent of patients discontinued tenapanor versus 1% in the sevelamer arm during the RTP. Adverse events during the 12-week RWP were similar between placebo and tenapanor. Rates of diarrhea were significantly lower during the 14-week safety extension trial for tenapanor, at 7%.

- ESRD-HD was a 219-patient, Phase III randomized, double-blind trial with two periods following a washout of phosphate binders. Patients were randomized 1:1:1 to tenapanor (Xphozah) 3 mg twice daily, tenapanor 10mg twice daily, or tenapanor 30mg twice daily during the 8-week randomized treatment period (RTP), followed by re-randomization to either placebo or their previous dose of tenapanor (Xphozah) during the 4-week randomized withdrawal period. The primary end point was mean change in serum phosphate over the 4-week withdrawal period for the tenapanor (Xphozah) group (using pooled data) versus the placebo group. In the ITT analysis set, there was a statically significant difference in the primary endpoint between the pool tenapanor group and placebo, mean difference of -0.72 mg/dl (0.07 vs 0.79, $p=0.003$ for tenapanor (Xphozah) and placebo, respectively). Any adverse events were slightly higher in the 30 mg tenapanor (Xphozah) group when compared to placebo in the RWP, 35.3% vs 25.6%, but serious adverse events were higher in the placebo arm, 4.9% vs 0% for all pooled tenapanor (Xphozah).
- NORMALIZE was an open-label 18-month extension study. Patients entering the study from the tenapanor (Xphozah) arm with serum phosphate levels in the normal range were followed with no medication changes. Patients entering the study from the tenapanor (Xphozah) arm with serum phosphate greater than 4.5 mg/dL had sevelamer tablets added incrementally to achieve normal serum phosphate levels. Patients entering the study from the sevelamer safety control arm had tenapanor (Xphozah) tablets added to their treatment regimen while reducing sevelamer tablets based on their serum phosphate value to achieve normal serum phosphate levels. The primary objective of the study was to evaluate the ability of tenapanor (Xphozah) alone or in combination with sevelamer to achieve serum phosphate levels within the normal range (2.5 to 4.5 mg/dL) in patients with CKD on maintenance dialysis whose serum phosphate levels were greater than 6.0 mg/dL at baseline.
- OPTIMIZE was a 26-week, randomized, open label study, which included 330 patients with CKD on maintenance dialysis with hyperphosphatemia evaluating treatment of hyperphosphatemia in adult patients with CKD on maintenance

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dialysis, with tenapanor (Xphozah) alone or in combination with phosphate binders, to achieve target serum phosphate ≤ 5.5 mg/dL. The study randomized patients on a stable dose of phosphate binder treatment with serum phosphate > 5.5 mg/dL and ≤ 10.0 mg/dL in a 1:1 ratio to two different treatment cohorts, as well as patients who were phosphate binder naïve with serum phosphate > 4.5 and ≤ 10.0 mg/dL in a third cohort.

- Results from NORMALIZE and OPTIMIZE are not yet published at this time.

VI. There are two commonly cited clinical practice guidelines for the management of CKD with threshold and guidance on target ranges for serum phosphate levels. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) 2003 practice guidelines recommend that pharmacological and non-pharmacological approaches be implemented to reduce serum phosphate levels below 5.5mg/dL in patients with CKD Stage 5 requiring dialysis. Within this clinical practice guideline, serum phosphate of > 5.5 mg/dL is consistent with hyperphosphatemia. Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of CKD-MBD (2017) recommend to lower elevated serum phosphate levels "toward the normal range" defined as a more stringent 2.5-4.5mg/dL in patients with CKD stages G3a to G5 to. This reference range is cited in part due to the observation that patients with serum phosphate levels close to 4.4 mg/dL had the best survival in observational/epidemiologic studies. The risk of mortality increases in a U-shape pattern from this point, as demonstrated in Block GA et al. (2004) with subsequent observational studies replicating similar findings.

- Block GA et Al. (2004) included 40,538 hemodialysis patients in an observational study which analyzed the relationship between serum phosphorus levels and risk of death. Patients were stratified into serum phosphorous categories of < 3 mg/dL, increasing by 1mg/dl groups until > 9 mg/dl. The study showed an increasing risk of death and hospitalization with each 1mg/dl increase in serum phosphorus above 5mg/dL. The RR were 1.10 (1.02 to 1.17) and 1.25 (1.18 to 1.33) for serum phosphorus concentrations 5.0 to 5.5 mg/dl and 5.5 to 6.0 mg/dl, respectively, and high serum phosphorus concentrations (≥ 11.0 mg/dl) were associated with even larger increases in RR (2.47; 95% CI, 1.90 to 3.19).
- A systematic review and meta-analysis by Palmer et al. consisting of 115,552 patients from 16 cohort studies between 1947 and 2010, evaluated the association between levels of serum phosphorus and risks of all-cause and cardiovascular mortality in patients with CKD. Thirteen studies assessed the relationship between serum phosphorus levels and all-cause mortality and 3 studies assessed serum phosphorus levels and CV mortality. The trial noted for every 1 mg/dL increase in serum phosphorus, the risk of mortality increased by 35% (RR 1.35; 95% CI, 1.16-1.57) in adequately adjusted studies, and by 18% (RR 1.18, 95% CI, 1.12-1.25) in the available 13 studies. The risk of CV mortality increased by 10% per 1 mg/dL increase in serum phosphorus (RR, 1.10; 95% CI, 1.06-1.13) in the 3 studies assessing CV mortality.

VII. The quality of evidence is considered low-moderate due to use of study outcomes that have not been directly correlated with improvements in clinically meaningful outcomes such as morbidity, mortality, symptom relief, health-related quality of life, or mental, physical, and emotional functioning. Nevertheless, reduction of phosphate levels in patients with hyperphosphatemia in CKD is an established goal of treatment and is accepted by the FDA as a validated surrogate endpoint based on observational studies that link high phosphate levels to

increased risk of death due to cardiovascular causes. It is not known whether tenapanor (Xphozah) improves morbidity or mortality at this time, however, as demonstrated in the AMPLIFY trial, it lowers phosphate to normal levels ($sP < 5.5 \text{ mg/dL}$) in 37.1% of patients at week 4 and provides consistent reduction in phosphate levels compared to placebo as demonstrated in PHREEDOM and ESRD-HD clinical trials.

- VIII. In addition to pharmacotherapy, clinical guidelines recommend limiting dietary phosphorus intake in the treatment of hyperphosphatemia, and it is reasonable to consider phosphorus sources (e.g., animal, vegetable, additives).
- IX. There are currently no head-to-head trials comparing the efficacy of tenapanor (Xphozah) to available phosphate binders on the market, and indirect comparison is confounded by different patient populations, study designs, and study parameters. Currently available phosphate lowering agents lower serum phosphate levels by roughly 1.5-2.2 mg/dL and remain the standard of care in patients with CKD undergoing dialysis treatment who require serum phosphate lowering. There are four major classes of agents that have been approved in the US to control serum phosphate levels in adults with CKD on dialysis, including calcium-based binders, sevelamer-based products, lanthanum carbonate, and iron-based binders. Although available phosphate binders have similar phosphorus lowering potential, treatment effect and tolerability can vary in the real-world setting. Due to established safety and efficacy of these agents as well as cost-effectiveness, trial of three phosphate binders is required prior to treatment with tenapanor (Xphozah), unless previously not tolerated, ineffective, or contraindicated. Calcium-based binders are generally not recommended as a first line treatment option due to higher risk of mortality compared to non-calcium-based binders and risks associated with calcium accumulation. Sevelamer and lanthanum carry a contraindication in bowel obstruction and should be used with caution in patients with gastrointestinal (G) disease or with major GI surgery. Sucroferric oxyhydroxide (Velphoro) and ferric citrate (Auryxia) are iron-based binders. There are no contraindications to treatment with sucroferric oxyhydroxide (Velphoro); however, ferric citrate (Auryxia) is contraindicated in iron overload syndromes. Sucroferric oxyhydroxide (Velphoro) is not systemically absorbed, therefore, iron-absorption is minimal. Ferric citrate (Auryxia) may increase serum iron, ferritin, and transferrin saturation (TSAT), which may lead to excessive elevations in iron stores. Serum iron, ferritin, and transferrin saturation (TSAT) should be monitored.
- X. Initial authorization is limited to 3 months of therapy as treatment response (e.g., sP lowering) is expected to occur as early as week 1 as shown from the data in AMPLIFY trials. Delayed treatment response beyond 3 months was not shown within the clinical program given the short trial duration of ESRD-HD (12 weeks) and AMPLIFY (4 weeks).

Investigational or Not Medically Necessary Uses

- I. Safety and efficacy have not yet been sufficiently established and/or clinical trials are currently underway for the following indications:
 - A. Non-dialysis dependent hyperphosphatemia in chronic kidney disease
 - B. Irritable bowel syndrome with diarrhea
 - C. Mixed irritable bowel syndrome
 - D. Chronic idiopathic constipation
 - E. Opioid-induced constipation

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
Tegaserod (Zelnorm) Policy	Irritable bowel syndrome with constipation (IBS-C)
Opioid-Induced Constipation Agents Policy	Opioid-induced constipation

Policy Implementation/Update:

Action and Summary of Changes	Date
Changed step therapy requirement for tenapanor (Xphozah) to require trial of three phosphate binders. Added tenapanor (Xphozah), indication for hyperphosphatemia in patients with CKD, and supporting evidence. Remove CKD and hyperphosphatemia from E/I section. Updated alternative requirements for IBS indication to include generic lubiprostone.	12/2023
Policy updated to include pre-requisites of trial of current formulary and preferred agents; removed criteria requiring documentation of pain scores and stool frequency; updated supporting evidence	03/2022
Policy created	02/2020

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP157

Description

Tetrabenazine (Xenazine), deutetrabenazine (Austedo) and valbenazine (Ingrezza/Ingrezza Sprinkle) are reversible vesicular monoamine transporter 2 (VMAT2) inhibitors that act by regulating monoamine uptake from the cytoplasm to the synaptic vesicle. Its mechanism of action in Tardive dyskinesia or chorea-reduction is unknown.

Length of Authorization

- Initial:
 - i. Tardive dyskinesia: Six months
 - ii. Chorea associated with Huntington's disease: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
tetrabenazine (Xenazine)	12.5 mg	Chorea associated with Huntington's disease	60 tablets/30 days
	25 mg		
	25 mg	Chorea associated with Huntington's disease, genotyped <i>extensive</i> and <i>intermediate metabolizers</i>	120 tablets/30 days
generic tetrabenazine	12.5 mg	Chorea associated with Huntington's disease	60 tablets/30 days
	25 mg		
	25 mg	Chorea associated with Huntington's disease, genotyped <i>extensive</i> and <i>intermediate metabolizers</i>	120 tablets/30 days
deutetrabenazine (Austedo)	6 mg	Tardive dyskinesia in adults; Chorea associated with Huntington's disease	210 tablets/30 days
	9 mg		60 tablets/30 days
	12 mg		120 tablets/30 days
deutetrabenazine (Austedo XR)	6mg, 12mg, 24mg titration tab kit	Tardive dyskinesia in adults; Chorea associated with Huntington's disease	42 tablets/28 days
	12mg, 18mg, 24mg, 30mg titration tab kit		28 tablets/28 days
	6 mg		60 tablets/30 days
	12 mg		30 tablets/30 days
	18 mg		60 tablets/30 days
	24 mg		60 tablets/30 days
	30 mg		30 tablets/30 days
	36 mg		30 tablets/30 days
	42 mg		30 tablets/30 days

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	48 mg		30 tablets/30 days
valbenazine (Ingrezza)	40 mg	Tardive dyskinesia; Chorea associated with Huntington's disease	30 capsules/30 days; 4-week Initiation Pack
	60 mg		
	80 mg		
valbenazine (Ingrezza Sprinkle)	40 mg	Tardive dyskinesia; Chorea associated with Huntington's disease	30 capsules/30 days
	60 mg		
	80 mg		

Initial Evaluation

- I. **Tetrabenazine (Xenazine), deutetrabenazine (Austedo) and valbenazine (Ingrezza/Ingrezza Sprinkle)** may be considered medically necessary when the following criteria below are met:
 - A. Member is 18 years of age or older; **AND**
 - B. Medication is prescribed by, or in consultation with, a neurologist or psychiatrist; **AND**
 - C. Medication will not be used in combination with another VMAT2 inhibitor [e.g. tetrabenazine (Xenazine), deutetrabenazine (Austedo) valbenazine (Ingrezza/Ingrezza Sprinkle)], monoamine oxidase inhibitor (MAOI) [e.g. isocarboxazid (Marplan®), phenelzine, tranylcypromine, reserpine]; **AND**
 - D. Provider attestation that member does not have uncontrolled symptoms of depression, agitation, psychosis, or increased risk of suicidality; **OR**
 1. Provider attestation that the potential benefit of treatment with VMAT2-I outweighs the risk of depression or suicidality; **AND**
 - E. A diagnosis of one of the following:
 1. **Chorea associated with Huntington's disease; AND**
 - i. For BRAND tetrabenazine (Xenazine) or generic tetrabenazine:
 - a. Provider attestation that doses exceeding 50mg per day are to be reserved for extensive and intermediate metabolizers (see quantity limit table based on metabolizer status); **AND**
 - i. If request is for BRAND tetrabenazine (Xenazine), treatment with generic tetrabenazine, deutetrabenazine (Austedo), and valbenazine (Ingrezza/Ingrezza Sprinkle) has been ineffective, contraindicated or not tolerated; **OR**
 2. **Tardive dyskinesia; AND**
 - i. The request is for generic tetrabenazine, valbenazine (Ingrezza/Ingrezza Sprinkle) and deutetrabenazine (Austedo); **AND**
 - ii. Member has failed to respond to a change or is unable to switch current antidopaminergic therapy
- II. Tetrabenazine (Xenazine), deutetrabenazine (Austedo), and Valbenazine (Ingrezza/Ingrezza Sprinkle) are considered investigational when used for all other conditions, including but not limited to:
 - A. Tourette's syndrome

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Member has exhibited improvement or stability of disease symptoms.

Supporting Evidence

- I. Safety and effectiveness of VMAT2 inhibitors have not been established in pediatric patients.
- II. Agents in this policy are required to be prescribed by or in consultation with a neurologist or psychiatrist considering the seriousness of adverse effects (depression and suicidality, cognitive decline, Parkinsonism, dysphagia, sedation/somnolence, akathisia, restlessness, and disability), complexity of the disease state, and dosing of the medication.
- III. Concomitant use of tetrabenazine (Xenazine), deutetrabenazine (Austedo), and valbenazine (Ingrezza/Ingrezza Sprinkle) with MAOIs may increase the concentration of monoamine neurotransmitters in synapses, potentially leading to increased risk of adverse reactions such as serotonin syndrome, or attenuated treatment effect. Tetrabenazine (Xenazine), deutetrabenazine (Austedo), and valbenazine (Ingrezza/Ingrezza Sprinkle) should not be used in combination with an MAOI.
- IV. The International Guidelines for the Treatment of Huntington's Disease recommend tetrabenazine (VMAT2-I) as first line for chorea management except for patients who have, "not well-managed depression or suicidal thoughts" due to the side effects of the drug class. In patients with psychiatric disorders or personality/behavioral disorders that increase suicide risk, the guidelines recommend the use of 2nd generation neuroleptics. Treatment with a single agent is preferred due to the risk of additional adverse effects. Additionally, compendia cites comorbid depression, agitation, and/or psychosis as criteria for determining whether a VMAT2-I is appropriate based on patient comorbidities.
- V. Per the Physician's Guide to the Management of Huntington's Disease 3rd edition, providers often treat chorea with neuroleptics (e.g., aripiprazole, haloperidol, fluphenazine, risperidone, olanzapine) based on clinical experience and due to safety concerns associated with VMAT2-inhibitors, namely: decreased cognition and mood, increased suicidality and depression. Studies of the anti-choreic effects of neuroleptics were excluded from the AAN guideline review due to criteria set forth; however, the AAN acknowledges neuroleptics are commonly used in clinical practice to treat chorea and recommends additional study in recognition of this use. In consideration of the Boxed Warnings and adverse effects associated with this class, a trial of therapy often considered in standards-of-care is reasonable.
- VI. KINECT-HD was a phase 3, randomized, double-blind, placebo-controlled trial which studied valbenazine (Ingrezza/Ingrezza Sprinkle) vs placebo for 12 weeks. The trial included 125 participants (valbenazine n=64, placebo n=61) with a moderate level of disease advancement per UHDRS TFC (Total Functional Capacity) scores for Huntington's chorea. The primary endpoint of the study was assessing the mean change in UHDRS-TMC (Unified Huntington's Disease Rating Scale –Total Maximal Chorea) from baseline to the end of the study at week 12.

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The results demonstrated a statistically and clinically significant improvement in the primary endpoint for valbenazine vs placebo (-4.6 vs 1.4, difference -3.2, 95% CI -4.4 to -2.0, $p < 0.0001$). The secondary endpoints included Clinical Global Impression of Change (CGI-C) and Patient Global Impression of Change (PGI-C) at week 12, and mean changes from baseline to week 12 in short-form Quality of Life in Neurological (NeuroQoL) Disorders Upper Extremity and Lower Extremity Function T-scores. By week 12, there was a statistically significant difference in the CGI-C and PGI-C scores compared to baseline ($p = .0007$, $p = 0.0062$). However, the new secondary measures within the study (NeuroQoL) indicated no statistically significant change when compared to placebo ($p = 0.3304$). In terms of safety, the results listed no worsening of anxiety, depression, akathisia, parkinsonism, or new reports of suicidal ideation.

- VII. No sufficient evidence was found to show superiority of one agent over the other.
- VIII. When clinically appropriate, the two main strategies of pharmacotherapy in patients who are showing signs of tardive dyskinesia include discontinuation of the offending drug and switching from a first- to a second-generation antipsychotic drug because second generation neuroleptics have a lower risk of TD.
- IX. Additional pharmacologic options [e.g. benzodiazepines, anticholinergic drugs (trihexyphenidyl, benztropine)] have been used in clinical practice for many years. AAN states use of benzodiazepines and tetrabenazine (Xenazine) as standard of care treatments is based on weak clinical evidence but it has been standard of care. According to the 2012 AAN guidelines, amantadine or riluzole could be other agents prescribed for chorea management (Level B).
- X. There is a lack of head-to-head trials and scientific evidence to show superiority of one medication over the other. There is history of use with tetrabenazine in tardive dyskinesia.
- XI. For patients with a diagnosis of TD, additional pharmacologic interventions include the use of benzodiazepines, botulinum toxin injections, or tetrabenazine (Xenazine) to control symptoms of TD, paradoxically, resuming treatment with antipsychotic drugs in order to suppress TD.

Investigational or Not Medically Necessary Uses

I. Tourette's syndrome

A. Tetrabenazine (Xenazine)

- A. VMAT2 inhibitors currently available in the United States include deutetrabenazine and valbenazine. Although both are being investigated in the treatment of TS, they, like tetrabenazine (Xenazine), are not yet approved by the US Food and Drug Administration (FDA).
- B. There is insufficient evidence to support the use of tetrabenazine (generic, Xenazine) for the treatment of other movement disorders, including, but not limited to dystonic tremor, or Tourette's syndrome.

B. Deutetrabenazine (Austedo)

- i. Deutetrabenazine (Austedo) is currently being investigated for use in Tourette's syndrome in:
 - a. A Pilot Study Of SD-809 (Deutetrabenazine) In Moderate To Severe Tourette Syndrome
 - b. A Randomized, Double-blind, Placebo-controlled Study of TEV-50717 (Deutetrabenazine) for the Treatment of Tourette Syndrome in Children and Adolescents

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- ii. Although deutetrabenazine (Austedo) is being studied for the treatment of Tourette's syndrome, there is currently no published evidence supporting its safety or efficacy in this setting.
- C. Valbenazine (Ingrezza/Ingrezza Sprinkle)
 - 1. Valbenazine (Ingrezza/Ingrezza Sprinkle) is currently being investigated for use in Tourette's syndrome; however, initial studies have not demonstrated efficacy for this condition.
 - i. In a phase 2 trial in pediatric patients with tics associated with Tourette's syndrome, valbenazine (Ingrezza/Ingrezza Sprinkle) did not meet the pre-specified primary endpoint of change from baseline between the placebo valbenazine (Ingrezza/Ingrezza Sprinkle) in the Yale Global Tic Severity Scale (YGTSS) at week six in the intent-to-treat population.
 - ii. Based on the above results, a second phase 2 trial will aim to evaluate a higher dose of valbenazine (Ingrezza/Ingrezza Sprinkle) to suppress tics in pediatric patients.
 - 2. Although valbenazine (Ingrezza/Ingrezza Sprinkle) is being studied for the treatment of Tourette's syndrome, there is currently no published evidence supporting its safety or efficacy in this setting.

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14. Safety and Efficacy of NBI-98854 (valbenazine) in Pediatric Subjects With Tourette Syndrome, ClinicalTrials.gov Identifier: NCT03530293, <https://clinicaltrials.gov/ct2/show/NCT03530293?term=valbenazine&draw=2&rank=7>

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Policy Implementation/Update:

Action and Summary of Changes	Date
Added Austedo XR 18mg tablet and titration kit (12mg, 18mg, 24mg, 30mg). Removal of 6mg, 12mg, 24mg titration tab kit, as it is exiting the market.	07/2024
Added 30mg, 36mg, 42mg, and 48mg Austedo XR tablets to table	06/2024
Added 60mg Ingrezza sprinkles to table	05/2024
Added Huntington's chorea indication for valbenazine (Ingrezza). Removed the step through generic tetrabenazine. Updated initial authorization for Tardive Dyskinesia indication to 6 months following standard authorization.	12/2023
Adding Austedo XR titration tablet kit	07/2023
Added Austedo XR to QL table	04/2023
Updated QL for 6mg and 9mg Austedo tablets; updated formatting	01/2023
- Updated criteria to policy format and combined separate policies into one - Generic tetrabenazine added to tardive dyskinesia criteria - For deutetrabenazine (Austedo) only: Treatment with generic tetrabenazine and valbenazine (Ingrezza) has been ineffective, contraindicated or not tolerated - Medication will not be used in combination with another VMAT2 inhibitor, monoamine oxidase inhibitor (MAOI) [e.g. isocarboxazid (Marplan®), phenelzine, tranylcypromine, reserpine], it is contraindicated	12/2019
Added Tardive Dyskinesia indication for deutetrabenazine (Austedo™)	09/2017
Updated question 5 for valbenazine (Ingrezza™) based on P&T recommendations	08/2017
Previous Reviews	05/2017; 06/2017; 09/2017; 08/2019; 12/2019;

Policy Type: PA

Pharmacy Coverage Policy: UMP279

Description

Tezepelumab (Tezspire) is a thymic stromal lymphopoietin (TSLP) blocker

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
tezepelumab (Tezspire)	Severe Asthma	210 mg/1.91 mL prefilled pen	1 prefilled pen/30 days
Provider Administered Agents*, **			
tezepelumab (Tezspire)	Severe Asthma	210 mg/1.91 mL prefilled syringe*	1 prefilled syringe/30 days

*Medical drug that requires administration by a healthcare professional and is not available for self-administration by the member, considered one of the excluded classes under the prescription benefit. Prefilled syringe is only FDA approved for provider administration.

**Certain groups have opted into the pharmacy benefit optimization (PBO) program in which case selected infused specialty medications will only be covered under the pharmacy benefit, and claims submitted under the medical benefit will be denied as provider liability. For more details, please reference: <https://www.modahealth.com/medical/injectables/>

Initial Evaluation

- I. **Tezepelumab (Tezspire)** may be considered medically necessary when the following criteria are met:
 - A. Member is 12 years of age or older; **AND**
 - B. The request is for tezepelumab (Tezspire) prefilled pen; **AND**
 - C. Medication is prescribed by, or in consultation with, a physician specializing in allergy, pulmonology, immunology, or ENT (ear, nose, throat); **AND**
 - D. The medication will not be used in combination with another monoclonal antibody for the treatment of asthma (e.g., Dupixent [dupilumab], Xolair [omalizumab], Fasenna [benralizumab], Nucala [mepolizumab], Cinqair [reslizumab], etc.); **AND**
 - E. A diagnosis of **severe asthma** when the following are met:
 1. Member has **SEVERE** asthma as defined by one of the following:
 - i. Symptoms throughout the day
 - ii. Nighttime awakenings, often 7x/week
 - iii. SABA (e.g., albuterol, levalbuterol) use for symptom control occurs several times per day
 - iv. Extremely limited normal activities
 - v. Lung function (percent predicted FEV1) <60%
 - vi. Exacerbations requiring oral systemic corticosteroids are generally more frequent and intense relative to moderate asthma; **AND**

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2. Member must have two or more exacerbations in the previous year requiring daily oral corticosteroids for at least 3 days (in addition to the regular maintenance therapy defined below); **AND**
3. Member is currently being treated with:
 - i. A medium- to high-dose, or maximally tolerated inhaled corticosteroid (ICS) [e.g., budesonide, fluticasone, mometasone]; **AND**
 - a. One additional asthma controller medication (e.g., long-acting beta-2 agonist [LABA] {e.g., Serevent Diskus}, long-acting muscarinic antagonist [LAMA] {e.g., Spiriva Respimat}); **OR**
 - ii. A maximally tolerated dose of ICS/LABA combination product (e.g., Advair, Airduo, Breo, Dulera, Symbicort); **AND**
4. Background controller medications (e.g., Advair, Airduo, Breo, Dulera, Symbicort) will be continued with the use of tezepelumab (Tezspire), unless all are contraindicated; **AND**
5. Member meets one of the following scenarios (i, ii, or iii):
 - i. Tezepelumab (Tezspire) will be used to treat severe asthma with an eosinophilic phenotype (i.e., blood eosinophils ≥ 150 cells/ μ L within the last 12 months); **AND**
 - a. Treatment with dupilumab (Dupixent) AND mepolizumab (Nucala) have been ineffective, contraindicated, or not tolerated; **OR**
 - ii. Tezepelumab (Tezspire) will be used to treat severe asthma with an allergic phenotype (i.e., serum total IgE level, measured before the start of treatment, of ≥ 30 IU/mL and ≤ 700 IU/mL); **AND**
 - a. Treatment with omalizumab (Xolair) has been ineffective, contraindicated, or not tolerated; **OR**
 - iii. Attestation that member does not have severe asthma with an eosinophilic or allergic phenotype.

II. Tezepelumab (Tezspire) is considered investigational when used for all other conditions, including but not limited to:

- A. Non-severe asthma
- B. Chronic obstructive pulmonary disease (COPD)
- C. Prurigo nodularis
- D. Eosinophilic esophagitis
- E. Chronic rhinosinusitis with nasal polyposis (CRSwNP)
- F. Atopic dermatitis

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**

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- III. Must not be used in combination with another monoclonal antibody (e.g., Dupixent [dupilumab], Xolair [omalizumab], Fasenra [benralizumab], Nucala [mepolizumab], Cinqair [reslizumab], etc.); **AND**
- IV. Member has exhibited improvement or stability of disease symptoms (e.g., reduced asthma exacerbations, FEV1, reduced systemic corticosteroid requirements, reduced hospitalizations); **AND**
- V. Background controller medications (e.g., ICS/LABA product listed above) will be continued with the use of tezepelumab (Tezspire) unless contraindicated.

Supporting Evidence

- I. Tezepelumab (Tezspire) is FDA approved as an add-on maintenance treatment for patients 12 years and older with severe asthma. Efficacy and safety in those under 12 years of age has not been evaluated in clinical trials.
- II. Tezepelumab (Tezspire) trials excluded concomitant biologic therapy; moreover, there is a lack of evidence supporting treatment with dual use of biologic therapies and a potential for increased risk of side effects.
- III. The Global Initiative for Asthma (GINA) 2022 guidelines define severe asthma as asthma that remains uncontrolled despite optimized treatment with high dose ICS-LABA, or that requires high dose ICS-LABA to prevent it from becoming uncontrolled. Severe asthma must be distinguished from asthma that is difficult to treat due to inadequate or inappropriate treatment, or persistent problems with adherence or comorbidities such as chronic rhinosinusitis or obesity as there are very different treatment implications compared with if asthma is relatively refractory to high dose ICS-LABA or even OCS. GINA guidelines recommend the addition of respiratory biologics after inadequate asthma control despite good adherence and inhaler technique on maximized Step 4 therapy (i.e., medium dose ICS-LABA and reliever therapy or medium or high dose ICS-LABA with as needed SABA).
- IV. The labeled indication for tezepelumab (Tezspire) is not dependent on the presenting phenotype for severe asthma. However, balancing the safety and efficacy of other respiratory biologics, trial of targeted eosinophilic or allergic asthma agents will be required prior to treatment with tezepelumab (Tezspire).
- V. Tezepelumab (Tezspire) was studied in two registrational, multicenter, randomized, double-blind, placebo-controlled trials – PATHWAY and NAVIGATOR. In both studies participants with severe asthma received tezepelumab (Tezspire) 210 mg or placebo subcutaneously once every four weeks for 52 weeks. The primary efficacy outcome in both trials was the annualized rate or asthma exacerbations (AAER). An asthma exacerbation was defined as worsening of asthma requiring the use of or increase in oral or injectable corticosteroids for at least 3 days, or a single depo-injection of corticosteroids, and/or emergency department visits requiring use of oral or injectable corticosteroids and/or hospitalization.
 - PATHWAY
 - i. PATHWAY (N=550) was a phase 2b, randomized, multicenter, double-blind, placebo-controlled trial. Participants were randomized 1:1:1:1 to receive tezepelumab (Tezspire) 70 mg, 210 mg, 280 mg, or placebo subcutaneously every four weeks. Baseline characteristics between the treatment groups

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were similar. Average age 51.6 years, 65.6% female, 92.5% white, average BMI 28, 49% on high dose ICS, ACQ-6 score 2.68, AQLQ 4.14, FEV1, and mean blood eosinophil counts 367 ± 361 for tezepelumab groups. The AAER, was found to be statistically significant for each dose compared to placebo.

- ii. The 210 mg group had the highest relative reduction compared to placebo. Secondary endpoints were statistically significant for the 210 mg dose; however, clinical significance was not realized. Reported endpoints were smaller than the minimal clinically important differences for the ACQ-6 and AQLQ(S) +12 scores (0.5-point difference on these scales) as well as the FEV1 (100 to 200mL difference).

PATHWAY	Placebo	Tezepelumab (210 mg)	Reported Differences (95% CI)	p-Value
AAER	0.72 (0.61, 0.86)	0.20 (0.14, 0.28)	71% (54, 82)	<0.001
FEV ₁ (ΔL)	-0.06	0.08	0.13 (0.03, 0.23)	0.009
ACQ-6	-0.91	-1.26	-0.36 (-0.58, -0.13)	0.002
AQLQ(S)+12	0.91	1.25	0.33 (0.09, 0.58)	0.008

- NAVIGATOR

- i. NAVIGATOR was a phase III, multicenter, randomized, double-blind, placebo-controlled study (N= 1,161). Baseline characteristics between the treatment groups were similar. Average age 49.5 years, 36.5% male, 62.2% white, average BMI 28.5, 75.1% on high dose ICS, ACQ-6 score 2.8, mean blood eosinophil count 340 (58.4% <300 cells/μL), and 68.5% had IgE positive disease.

NAVIGATOR	Tezepelumab 210 mg	Placebo	Reported Differences (95% CI)	p-Value
Overall Population				
FEV1 (Δ L)	0.23	0.09	0.13 (0.08 to 0.18)	<0.001
ACQ-6	-1.55	-1.22	-0.33 (-0.46 to -0.20)	<0.001
AQLQ(S) +12	1.49	1.15	0.34 (0.20 to 0.47)	<0.001
ASD	-0.71	-0.59	-0.12 (-0.19 to -0.04)	0.002
Blood Eosinophils <150 cells/μL				
FEV1 (Δ L)	0.10	0.07	0.03 (-0.07 to 0.13)	-
ACQ-6	-1.17	-1.08	-0.09 (-0.33 to 0.16)	-
AQLQ(S) +12	1.07	0.96	0.11 (-0.16 to 0.37)	-
ASD	-0.53	-0.53	(-0.15 to 0.15)	-

- ii. The AAER in the overall population was 0.93 (95% CI; 0.80 to 1.07) in the tezepelumab group and 2.10 (95% CI; 1.84 to 2.39) in the placebo group (RR, 0.44 (95% CI; 0.37 to 0.53; p<0.001). For patients with a blood eosinophil count of < 300 cells/μL the AAER was 1.02 (95% CI, 0.84 to 1.23) in the tezepelumab group and 1.73 (95% CI, 1.46 to 2.05) in the placebo group (RR, 0.59; 95% CI, 0.46 to 0.75; p<0.001).
- iii. Secondary endpoints were all found to be statistically significant; however, minimal clinically important differences were not met to warrant clinical significance for the ACQ-6 and AQLQ(S)+12 in the overall population. Secondary endpoints did not reach statistical significance in the <150 cells/μL subgroup.
- The quality of evidence for tezepelumab (Tezspire) is considered moderate. There is data to support statistically significant reductions in AAER and secondary endpoints; however, not all endpoints were found to meet the minimal clinically important differences. Subpopulation analysis in those with blood eosinophils <150 cells/μL

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did not reach statistically significant differences compared to placebo for secondary endpoints. Only 80 adolescent trial participants were included in the registrational trials which may reduce generalizability. Non-white populations were not adequately represented. There is uncertainty in how this therapy will perform head-to-head against other biologics.

VI. Tezepelumab (Tezspire) was studied in a phase 3 oral corticosteroid sparing study (SOURCE). That ran parallel with the NAVIGATOR study.

- SOURCE was a multicenter, randomized, double-blind, placebo-controlled, parallel group trial to evaluate the efficacy and safety of the medication in reducing oral corticosteroid use in adults with oral corticosteroid dependent asthma. The study ran for 48 weeks in 150 adult patients. Participants also had to be treated with ICS and a long-acting beta 2 agonist along with chronic treatment with oral corticosteroids (OCS).
- Study protocol was published but not the study results themselves; however, AstraZeneca released a statement in December of 2020 that the primary endpoint, significant reduction in the daily OCS dose, without loss of asthma control, with tezepelumab compared to placebo was not met (odds ratio [OR] 1.28, 95% CI 0.69 to 2.35). However, safety profile was reported to be consistent with previous trials.

VII. Patients who completed the NAVIGATOR or SOURCE studies had the opportunity to enroll in DESTINATION, a phase 3 long-term extension study aiming to evaluate the safety and efficacy of tezepelumab over a period of up to 2 years (inclusive of the treatment period of either predecessor study).

- The primary objective of DESTINATION is to assess the long-term safety and tolerability of tezepelumab compared with placebo. For individuals who initially received tezepelumab (n=528) in NAVIGATOR, incidence of adverse events over 104 weeks was 49.62 (95% CI 45.16 to 54.39) per 100 patient-years, compared with 62.66 (56.93 to 68.81) for those receiving placebo (n=531; difference -13.04, 95% CI -17.83 to -8.18). For serious adverse events, incidence was 7.85 (6.14 to 9.89) per 100 patient-years for individuals who initially received tezepelumab and 12.45 (9.97 to 15.35) for those who received placebo (difference -4.59, -7.69 to -1.65). Incidence of serious adverse events was 13.14 (7.65 to 21.04) per 100 patient-years for those who initially received tezepelumab and 17.99 (10.66 to 28.44) for those who received placebo (difference -4.85, -14.88 to 4.53). Tezepelumab reduced the annualized asthma exacerbation rate over 104 weeks compared with placebo. In participants initially from NAVIGATOR, the annualized asthma exacerbation rate ratio over 104 weeks was 0.42 (95% CI 0.35 to 0.51).

VIII. Tezepelumab (Tezspire) was approved for self-administration in February 2023 based on results from the PATHFINDER clinical trial program which included PATH-BRIDGE (phase 1) and PATH-HOME (phase 3).

- PATH-HOME was a phase 3, multicenter, randomized, open-label, parallel-group study where 216 patients were randomized to receive tezepelumab (Tezspire) via a pre-filled syringe (N=111) or an autoinjector (N=105). Under the trial protocol the first, second, third and final doses were administered in the clinic (weeks 0, 4 and 8), the fourth and fifth doses were administered at home (weeks 12 and 16), and the

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sixth and final dose was administered in clinic (week 20). The primary endpoint was the proportion of successful administrations of tezepelumab (Tezspire).

- Baseline demographics and clinical characteristics in both device groups were representative of the targeted clinical population. Median age was 47.2 (18.2) years – 24 adolescent patients were included, 50% were female, mean duration of asthma was 20.1 (15.5) years, mean ACQ-6 baseline was 2.23 (0.73) in the PFS group and 2.08 (0.62) in the AI group.
- Tezepelumab (Tezspire) was successfully administered via a PFS by 91.7% of the participants (100/109) and via AI by 92.4% (97/105). Overall, 95.4–97.1% of at-home administrations were successful across device groups. Malfunction occurred in 6 of 655 dispensed APFSs and 5 of 624 dispensed AIs. Of the six APFSs reported as malfunctioning three were used in the clinic (two by HCPs and one by a patient) and three were used at home (two by patients and one by a caregiver). In the AI group, all five devices reported as malfunctioning were used in the clinic by patients (no devices were reported as malfunctioning during at-home use). No mechanical or design-related issues were found during in vitro evaluation of the devices that were reported as malfunctioning.

- IX. There is a lack of strong scientific evidence from randomized controlled trials supporting safety and efficacy for an increased dosing frequency.

Investigational or Not Medically Necessary Uses

- I. Tezepelumab (Tezspire) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
- A. Non-severe asthma
 - B. Chronic obstructive pulmonary disease (COPD)
 - C. Prurigo nodularis
 - D. Eosinophilic esophagitis
 - E. Chronic rhinosinusitis with nasal polyposis (CRSwNP)

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
dupilumab (Dupixent®) Policy	Asthma (moderate to severe)
	Atopic Dermatitis (moderate to severe)
	Chronic rhinosinusitis with nasal polyposis
	Eosinophilic esophagitis
	Prurigo nodularis
omalizumab (Xolair®) Policy	Allergic asthma
	Chronic rhinosinusitis with nasal polyposis (CRSwNP)
	Chronic idiopathic urticaria (CIU)
benralizumab (Fasenra Pen™) Policy	Asthma (severe)
mepolizumab (Nucala®)	Asthma (severe)
	Eosinophilic granulomatosis with polyangiitis
	Hypereosinophilic Syndrome
	Chronic Rhinosinusitis with Nasal Polyps
reslizumab (Cinqair®) Policy	Asthma (severe)

Policy Implementation/Update:

Action and Summary of Changes	Date
Added to PBO program	10/2023
Policy created	05/2023

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP169

Description

Avatrombopag (Doptelet®), eltrombopag olamine (Promacta®), eltrombopag choline (Alvaiz®), lusutrombopag (Mulpleta®) are thrombopoietin (TPO) receptor agonists that induce the proliferation and differentiation of megakaryocytic progenitor cells from hematopoietic stem cells and megakaryocyte maturation, thus resulting in an increased production of platelets.

Fostamatinib (Tavalisse™) is a tyrosine kinase inhibitor (TKI) with activity against spleen tyrosine kinase (SYK). Fostamatinib metabolite, R406, inhibits signal transduction of Fc-activating receptors, B-cell receptors, and reduces antibody-mediated destruction of platelets.

Length of Authorization

- Initial:
 - **Avatrombopag (Doptelet)**
 - Thrombocytopenia associated with chronic liver disease, prior to planned procedure: one month
 - Chronic immune thrombocytopenia (ITP): Three months
 - **Eltrombopag olamine (generic and brand Promacta)**
 - Chronic thrombocytopenia due to chronic hepatitis C: three months
 - Chronic Immune Thrombocytopenia (ITP): three months
 - First-line treatment severe aplastic anemia: six months
 - Severe aplastic anemia, refractory: four months
 - **Eltrombopag choline (Alvaiz)**
 - Chronic thrombocytopenia due to chronic hepatitis C: three months
 - Persistent or Chronic thrombocytopenia (ITP): Three months
 - Severe aplastic anemia, refractory: four months
 - **Lusutrombopag (Mulpleta)**
 - Thrombocytopenia associated with chronic liver disease, prior to planned procedure: one month
 - **Fostamatinib (Tavalisse)**
 - Chronic Immune Thrombocytopenia (ITP): three months
- Renewal:
 - i. **Avatrombopag (Doptelet), eltrombopag olamine (generic and brand Promacta), eltrombopag choline (Alvaiz), and fostamatinib (Tavalisse)**
 - Chronic Immune Thrombocytopenia (ITP), refractory severe aplastic anemia, chronic thrombocytopenia due to chronic hepatitis C: six months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
avatrombopag (Doptelet)	Thrombocytopenia associated with chronic liver disease, prior to planned procedure	20 mg tablet	15 tablets/ 30 days
	Chronic Immune Thrombocytopenia (ITP)		60 tablets/30 days
eltrombopag olamine (generic and brand Promacta)	Severe aplastic anemia	12.5 mg/1 packet	[2 to 5 Years of age] 2.5mg/kg/day [6 to 11 Years of age] 30 packets/30 days (3 kits/30 days) [12 years and older] 30 packets/30 days (6 kits/30 days)
		25 mg/1 packet	[2 to 5 Years of age] 2.5mg/kg/day [6 to 11 Years of age] 90 packets/30 days (3 kits/30 days) [12 years and older] 180 packets/30 days (6 kits/30 days)
		12.5 mg tablet	30 tablets/ 30 days
		25 mg tablet	30 tablets/ 30 days
		50 mg tablet	30 tablets/ 30 days
		75 mg tablet	60 tablets/ 30 days
	Chronic thrombocytopenia due to chronic Hepatitis C	12.5 mg/1 packet	30 packets/ 30 days (4 kits/30 days)
		25 mg/1 packet	120 packets/30 days (4 kits/30 days)
		12.5 mg tablet	30 tablets/ 30 days
		25 mg tablet	30 tablets/ 30 days
		50 mg tablet	60 tablets/ 30 days
	Persistent or Chronic immune thrombocytopenia (ITP)	75 mg tablet	30 tablets/ 30 days
		12.5 mg/1 packet	30 packets/30 days (3 kits/30 days)
		25 mg/1 packet	90 packets/30 days (3 kits/30 days)
		12.5 mg tablet	30 tablets/ 30 days
		25 mg tablet	
		50 mg tablet	
		75 mg tablet	
lusutrombopag (Mulpleta)	Thrombocytopenia associated with chronic liver disease, prior to planned procedure	3 mg tablet	7 tablets/ 365 days

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fostamatinib (Tavalisse)	Chronic Immune Thrombocytopenia	100 mg tablets	60 tablets/30 days
		150 mg tablets	
eltrombopag Choline (Alvaiz)	Persistent or Chronic Immune Thrombocytopenia	9 mg tablet	30 tablets/30 days
		18 mg tablet	30 tablets/30 days
		36 mg tablet	30 tablets/30 days
		54 mg tablet	30 tablets/30 days
	Chronic Hepatitis C Thrombocytopenia	9 mg tablet	60 tablets/30 days
		18 mg tablet	60 tablets/30 days
		36 mg tablet	30 tablets/30 days
		54 mg tablet	30 tablets/30 days
	Severe Aplastic Anemia (refractory)	9 mg tablet	60 tablets/30 days
		18 mg tablet	60 tablets/30 days
		36 mg tablet	60 tablets/30 days
		54 mg tablet	60 tablets/30 days

Initial Evaluation

- I. **Avatrombopag (Doptelet), generic eltrombopag olamine, eltrombopag olamine (Promacta), eltrombopag choline (Alvaiz), lusutrombopag (Mulpleta) and fostamatinib (Tavalisse)** may be considered medically necessary when the following criteria below are met:
 - A. Medication is prescribed by, or in consultation with, a hematologist or gastroenterologist; **AND**
 - B. Medication is not used in combination with another thrombopoietin (TPO) receptor agonists (e.g. avatrombopag, eltrombopag, lusutrombopag); **AND**
 - C. A diagnosis of one of the following:
 1. **Chronic liver disease (CLD)-associated thrombocytopenia; AND**
 - i. Member is 18 years of age or older; **AND**
 - ii. Member has a platelet count less than $50 \times 10^9/L$; **AND**
 - iii. Request is for avatrombopag (Doptelet) OR lusutrombopag (Mulpleta); **AND**
 - a. Member is scheduled to undergo an invasive procedure that carries an intermediate-to-high risk of bleeding (e.g. spinal surgery, cardiac surgery, large polypectomy, or liver biopsy); **OR**
 - iv. Member has a diagnosis of **chronic Hepatitis C infection; AND**
 - a. Member is unable to initiate or maintain interferon-based treatment [eg. pegylated interferon (Pegasys®) and ribavirin]; **AND**
 - b. Request is for generic eltrombopag olamine or eltrombopag choline (Alvaiz); **OR**
 - c. Request is for brand eltrombopag olamine (Promacta); **AND**
 - i. Generic eltrombopag olamine or eltrombopag choline (Alvaiz) has been ineffective, not tolerated, or contraindicated; **OR**
 2. **Persistent or Chronic Immune Thrombocytopenia; AND**

- i. Treatment with first-line therapies (e.g corticosteroids, immunoglobulins, or splenectomy) have been ineffective, contraindicated, or not tolerated; **AND**
- ii. Member has a platelet count that is less than $30 \times 10^9/L$ with symptoms of bleeding; **AND**
- iii. Member is one year of age or older; **AND**
 - a. Request is for generic eltrombopag olamine or eltrombopag choline (Alvaiz); **OR**
 - b. Request is for brand eltrombopag olamine (Promacta); **AND**
 - i. Generic eltrombopag olamine or eltrombopag choline (Alvaiz) has been ineffective, not tolerated, or contraindicated); **OR**
- iv. Member is 18 years of age or older; **AND**
 - a. Request is for avatrombopag (Doptelet); **OR**
 - b. Request is for fostamatinib (Tavalisse); **OR**
- i. **Severe aplastic anemia; AND**
 - i. Member has met at least two of the following three criteria:
 - 1. Absolute neutrophil count (ANC) less than 500/microL; **OR**
 - 2. Platelet count less than 20,000/microL; **OR**
 - 3. Absolute reticulocyte count (ARC) less than 60,000/microL; **AND**
 - ii. Member has NOT received prior immunosuppressive therapy (IST) (e.g., request as first-line); **AND**
 - a. Member is two years of age or older; **AND**
 - b. Treatment will be initiated concurrently with immunosuppressive therapy (e.g., horse antithymocyte globulin (h-ATG) and cyclosporine); **AND**
 - c. The request is for generic eltrombopag olamine; **OR**
 - d. The request is for brand eltrombopag olamine (Promacta); **AND**
 - a. Generic eltrombopag olamine has been ineffective, not tolerated, or contraindicated; **OR**
 - iii. Member has severe aplastic anemia with refractory thrombocytopenia; **AND**
 - a. Treatment with at least one course of horse or rabbit anti-thymocyte globulin (ATG) and cyclosporine A (CSA) has been ineffective, contraindicated or not tolerated; **AND**
 - b. Request is for generic eltrombopag olamine or eltrombopag choline (Alvaiz); **OR**
 - c. Request is for brand eltrombopag olamine (Promacta); **AND**
 - a. Generic eltrombopag olamine or eltrombopag choline (Alvaiz) has been ineffective, not tolerated, or contraindicated

- II. Avatrombopag (Doptelet) is considered investigational when used for all other conditions, including but not limited to:
 - A. Chemotherapy-induced thrombocytopenia in adults with active non-hematological cancers
- III. Eltrombopag olamine (Promacta) is considered investigational when used for all other conditions, including but not limited to:
 - A. Elderly patients with Acute Myeloid Leukemia receiving induction chemotherapy
 - B. Prevention of chemotherapy induced thrombocytopenia
 - C. Thrombocytopenia with chronic HBV infection
 - D. Thrombocytopenia after consolidation therapy in acute myeloid leukemia (AML)
 - E. Thrombocytopenia associated with myelodysplastic syndrome
- IV. Eltrombopag choline (Alvaiz) is considered investigational when used for all other conditions, including but not limited to:
 - A. Myelodysplastic syndromes: thrombocytopenia, monotherapy in adult patients
 - B. Acute Myeloid Leukemia in adults
- V. Lusutrombopag (Mulpleta) is considered investigational when used for all other conditions.
- VI. Fostamatinib (Tavalisse) is considered investigational when used for all other conditions, including but not limited to:
 - A. Malignancies:
 - 1. Advanced colorectal, non-small cell lung, head and neck hepatocellular and renal cell carcinomas, and pheochromocytoma and thyroid tumors
 - 2. B-cell Lymphoma
 - 3. Large B-Cell Lymphoma
 - 4. Ovarian Cancer
 - 5. T-Cell Lymphoma
 - B. Rheumatoid Arthritis (RA)
 - C. Renal Transplant Rejection (antibody mediated rejection)
 - D. Chronic Graft vs. Host Disease

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Member has exhibited improvement or stability of disease symptoms; **AND**
 - A. **Chronic thrombocytopenia due to chronic Hepatitis C; AND**
 - 1. Member is unable to initiate or maintain interferon-based treatment [e.g. pegylated interferon (Pegasys®) and ribavirin]; **OR**
 - B. **Persistent or Chronic Immune Thrombocytopenia; AND**
 - 1. Platelet count has increased to greater than or equal to $50 \times 10^9/L$; **OR**
 - C. **Severe aplastic anemia; AND**

1. Absolute neutrophil count (ANC) less than 500/microL at baseline; **AND**
 - i. ANC has increased 100%; **OR**
 - ii. An ANC increase greater than or equal to 500/microL; **OR**
2. Platelet count was less than 20,000/microL at baseline; **AND**
 - i. Increase in platelet count has been greater than or equal to 20,000/microL from baseline; **OR**
 - ii. Stable platelet counts with transfusion independence for ≥ 8 weeks; **OR**
3. Absolute reticulocyte count (ARC) less than 60,000/microL at baseline; **AND**
 - i. There has been an increase in hemoglobin by 1.5 g/dL; **OR**
 - ii. In patients receiving transfusions, there has been a reduction in red blood cell transfusions; **AND**
- IV. If the request is for brand eltrombopag olamine (Promacta): Generic eltrombopag olamine or eltrombopag choline (Alvaiz) has been ineffective, not tolerated, or contraindicated

Supporting Evidence

- I. The clinical trials for avatrombopag (Doptelet), eltrombopag olamine (Promacta), eltrombopag choline (Alvaiz), lusutrombopag (Mulpleta), and fostamatinib (Tavalisse) did not include patients who were concomitantly using another TPO receptor agonists. Due to this, there is no data to assess the safety and efficacy of these agents when used concomitantly.
- II. Considering the complexity of the indications and agents, they must be prescribed by, or in consultation with, a hematologist or gastroenterologist.
- III. The safety and efficacy clinical trials of avatrombopag (Doptelet), eltrombopag olamine (Promacta), eltrombopag choline (Alvaiz), and lusutrombopag (Mulpleta) for chronic liver disease (CLD)-associated thrombocytopenia, did not include patients younger than 18 years of age. Therefore, there is no clinical trial data to support the use of these agents in pediatric patients.
- IV. Avatrombopag (Doptelet), eltrombopag olamine (Promacta) and eltrombopag choline (Alvaiz), and lusutrombopag (Mulpleta), for chronic liver disease (CLD)-associated thrombocytopenia, were studied in patients with a platelet count less than $50 \times 10^9/L$. This is because the risk for serious bleeding does not occur until the platelet count becomes very low—less than $10 \times 10^9/L$ or $20 \times 10^9/L$, with the risk for mild bleeding occurring when the platelet count is less than $50 \times 10^9/L$. These agents should not be administered to patients with chronic liver disease, without associated thrombocytopenia or risk of surgical bleed, in an effort to normalize platelet counts (normal platelet count in adults ranges from $150 \times 10^9/L$ to $450 \times 10^9/L$).
- V. Avatrombopag (Doptelet) and lusutrombopag (Mulpleta) are indicated for the treatment of thrombocytopenia in adults with chronic liver disease who are scheduled to undergo a procedure that carries an intermediate-to-high risk of bleeding (e.g. spinal surgery, cardiac surgery, large polypectomy, liver biopsy). They should not be administered to patients with chronic liver disease, without associated thrombocytopenia or risk of surgical bleed, in an effort to normalize platelet counts (normal platelet count in adults ranges from $150 \times 10^9/L$ to $450 \times 10^9/L$).
- VI. Eltrombopag olamine (Promacta) and eltrombopag choline (Alvaiz) are indicated for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. It should be used only in patients with chronic

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hepatitis C whose degree of thrombocytopenia prevents the initiation of interferon-based therapy or limits the ability to maintain interferon-based therapy. It should not be used to normalize platelet counts outside of this indication (normal platelet count in adults ranges from $150 \times 10^9/L$ to $450 \times 10^9/L$).

- VII. There is no safety and efficacy data to show superiority of one formulation over the other. The effectiveness of eltrombopag choline (Alvaiz) has been established based on adequate and well-controlled studies of eltrombopag olamine (Promacta) in adult and pediatric patients 6 years and older with persistent or chronic ITP, adult patients with chronic hepatitis C-associated thrombocytopenia, and adult patients with severe refractory aplastic anemia. In November 2023, Alvaiz was approved under the FDA accelerated approval 505(b)(2) process. The fundamental differences between the two salt forms: choline and olamine, respectively are the cost-effectiveness, dosage formulations, and differences of indications in both adult and patient populations. Eltrombopag choline (Alvaiz) has a reduced food effect therefore influencing the overall bioavailability for a patient in comparison to Eltrombopag olamine (Promacta). Per the package insert Alvaiz cannot be substituted with another eltrombopag product on a milligrams per milligrams basis. Although Alvaiz has reduced food effect, and therefore slightly increased bioavailability, the overall therapeutic effect remains similar to Promacta. This is reinforced by the package insert guidance to retain the same strict reduction of calcium intake ($<50\text{mg}$) and to refrain from administering Alvaiz 2 hours prior to and/or 4 hours post consumption of calcium and/or supplements containing polyvalent cations.
- VIII. Avatrombopag (Doptelet), eltrombopag olamine (Promacta) and eltrombopag choline (Alvaiz), and fostamatinib (Tavalisse) are indicated for the treatment of patients with chronic immune thrombocytopenia who have had an insufficient response to a first-line treatment (e.g. corticosteroids, immunoglobulins, or splenectomy).
- IX. According to American Society of Hematology 2019 clinical guidelines thrombopoietin receptor agonists such as Eltrombopag olamine (Promacta) are considered second line therapy for management of immune thrombocytopenia.
- X. Patients with platelet counts less than $30 \times 10^9/L$ were included in clinical trials for avatrombopag (Doptelet), eltrombopag olamine (Promacta), eltrombopag choline (Alvaiz), and fostamatinib (Tavalisse).
- XI. The efficacy and safety of eltrombopag olamine (Promacta) in pediatric patients one year and older with chronic ITP were evaluated in two double-blind, placebo-controlled trials. The trials differed in time since ITP diagnosis: at least 6 months versus at least 12 months. The primary endpoint was participants who achieved a platelet count greater than, or equal to, $50 \times 10^9/L$ for at least six out of eight weeks, generally seen between weeks five and 12. Pediatric patients (75%) treated with eltrombopag olamine (Promacta), compared with placebo (21%), saw an increased value with at least one platelet count greater than, or equal to, $50 \times 10^9/L$ during the first 12 weeks of randomized treatment in absence of rescue therapy. Platelet response to eltrombopag olamine (Promacta) was consistent across the age cohorts. Fewer pediatric patients treated required rescue treatment during the randomized, double blind period compared with placebo-treated patients (13% [6/45] versus 50% [11/22]).
 - a. The safety and effectiveness of eltrombopag choline (Alvaiz) has not been established in pediatric patients less than 6 years of age with persistent or chronic ITP. Pediatric patients must be able to swallow eltrombopag choline (Alvaiz) tablets whole.

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- XII. The safety and efficacy clinical trials of avatrombopag (Doptelet) and fostamatinib (Tavalisse), for chronic ITP, did not include patients younger than 18 years of age.
 - Fostamatinib (Tavalisse) is not recommended for use in patients less than 18 years of age because adverse effects on actively growing bones were observed in nonclinical studies. In subchronic, chronic, and carcinogenicity studies, chondrodystrophy of the femoral head was seen in rodents.
- XIII. Eltrombopag olamine (Promacta) is indicated in combination with standard immunosuppressive therapy for the first-line treatment of severe aplastic anemia and of patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy. Eltrombopag choline (Alvaiz) does not share this indication with eltrombopag olamine (Promacta).
- XIV. According to aplastic anemia & MDS international foundation (AAMDS) for a confirmed diagnosis of aplastic anemia the patient has to have met at least two of the following cell counts: absolute neutrophil count (ANC) less than 500/microL, platelet count less than 20,000/microL, or absolute reticulocyte count (ARC) less than 60,000/microL.
- XV. Thirty-four patients, two to 16 years of age, were enrolled in Study US01T. The primary outcome was rate of complete hematologic response at six months. In the D1-M6 cohort, 7 and 17 out of 25 pediatric patients achieved a complete and overall response, respectively, at six months.
- XVI. Ninety-two patients were enrolled in a prospective phase 1-2 study of immunosuppressive therapy plus eltrombopag olamine (Promacta). The three consecutively enrolled cohorts differed regarding the timing of initiation and the duration of the eltrombopag olamine (Promacta) regimen (cohort 1 received eltrombopag olamine (Promacta) from day 14 to six months, cohort 2 from day 14 to three months, and cohort 3 from day one to six months). The primary outcome was complete hematologic response at 6 months. Secondary end points included overall response, survival, relapse, and clonal evolution to myeloid cancer. The rate of complete response at 6 months was 33% in cohort 1, 26% in cohort 2, and 58% in cohort 3. The overall response rates at 6 months was 80% cohort 1, 87% cohort 2, and 94% cohort 3. The addition of eltrombopag olamine (Promacta) to immunosuppressive therapy (e.g. horse antithymocyte globulin (h-ATG) and cyclosporine) was associated with higher rates of hematologic response among patients with severe aplastic anemia than in a historical cohort.
- XVII. Eltrombopag olamine (Promacta) and eltrombopag choline (Alvaiz) was studied in a single-arm, single-center, open-label trial in 43 patients with severe aplastic anemia who had an insufficient response to at least one prior immunosuppressive therapy.
- XVIII. Eltrombopag olamine (Promacta) and eltrombopag choline (Alvaiz) is indicated for the treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. It should be used only in patients with chronic hepatitis C whose degree of thrombocytopenia prevents the initiation of interferon-based therapy or limits the ability to maintain interferon-based therapy. It should not be used to normalize platelet counts (normal platelet count in adults ranges from $150 \times 10^9/L$ to $450 \times 10^9/L$).
- XIX. Treatment with avatrombopag (Doptelet), eltrombopag olamine (Promacta), eltrombopag choline (Alvaiz), and fostamatinib (Tavalisse) should be discontinued after 12 weeks (three months) of treatment if platelet counts do not increase to a level sufficient to avoid clinically important bleeding (greater than or equal to $50 \times 10^9/L$ – risk for serious bleeding doesn't occur).

until the count becomes very low—less than $10 \times 10^9/L$ or $20 \times 10^9/L$, and for mild bleeding when the count is less than $50 \times 10^9/L$). These agents should not be administered to patients with chronic liver disease, that do not meet this criterion, in an effort to normalize platelet counts (normal platelet count in adults ranges from $150 \times 10^9/L$ to $450 \times 10^9/L$).

- XX. In the clinical trial, the primary end point was hematologic response at three to four months and defined as uni- or multilineage recovery by one or more of the following criteria: (1) platelet response (increase to $20 \times 10^3/\mu L$ above baseline or stable platelet counts with transfusion independence for a minimum of 8 weeks in those who were transfusion dependent on entry into the protocol); (2) erythroid response (when pretreatment hemoglobin was <9 g/dL, defined as an increase in hemoglobin by 1.5 g/dL or, in transfused patients, a reduction in the units of packed red blood cell transfusions by an absolute number of at least 4 transfusions for 8 consecutive weeks, compared with the pretreatment transfusion number in the previous 8 weeks); and (3) neutrophil response (when pretreatment absolute neutrophil count [ANC] of $<0.5 \times 10^3/\mu L$ as at least a 100% increase in ANC, or an ANC increase $>0.5 \times 10^3/\mu L$, and the toxicity profile as measured using Common Terminology Criteria for Adverse Events).
- XXI. Generic formulations of eltrombopag olamine (both tablets and oral suspension) are now commercially available for treating thrombocytopenia associated with chronic hepatitis C, severe aplastic anemia, and immune thrombocytopenia. Requiring treatment with generic eltrombopag olamine or eltrombopag choline (Alvaiz) prior to approval of brand eltrombopag olamine (Promacta) is clinically appropriate and cost-effective.

Investigational or Not Medically Necessary Uses

- I. Avatrombopag (Doptelet)
 - A. Chemotherapy-Induced Thrombocytopenia in adults with active non-hematological cancers
 - i. A randomized, double-blind, placebo-controlled study with an open-label extension to evaluate the efficacy and safety of avatrombopag (Doptelet) for the treatment of chemotherapy-induced thrombocytopenia in subjects with active non-hematological cancers is still recruiting.
 - B. There is limited or no published clinical trial data to support the use of avatrombopag (Doptelet) in conditions other than thrombocytopenia associated with chronic liver disease prior to planned procedure and chronic immune thrombocytopenia (ITP).
- II. Eltrombopag olamine (Promacta) and eltrombopag choline (Alvaiz)
 - A. Elderly Patients with Acute Myeloid Leukemia receiving induction chemotherapy (EPAG2015)
 - i. A Phase II, randomized, placebo-controlled study to assess the impact on outcome of eltrombopag (Promacta) administered to elderly patients with acute myeloid leukemia receiving induction chemotherapy in 110 participants and is still recruiting.
 - B. Prevention of chemotherapy induced thrombocytopenia
 - i. A phase I/II open-label study of eltrombopag for the prevention of chemotherapy induced thrombocytopenia (CIT) in subjects with advanced soft tissue and bone sarcomas receiving gemcitabine and docetaxel chemotherapy was terminated.
 - C. Thrombocytopenia with chronic HBV infection

- i. A multicenter, single-arm, open-label study in 58 participants to evaluate the efficacy and safety of eltrombopag for thrombocytopenia in Chinese patients with chronic HBV infection is still recruiting.
- D. Thrombocytopenia after consolidation therapy in acute myeloid leukemia (AML)
 - i. Randomized, single arm, single-blind study in 220 participants of eltrombopag (Promacta) and eltrombopag choline (Alvaiz) in thrombocytopenia after consolidation therapy in acute myeloid leukemia (AML) is in recruiting stage.
- E. Thrombocytopenia associated with myelodysplastic syndrome
 - i. In a three-part study of eltrombopag in thrombocytopenic subjects with myelodysplastic syndromes or acute myeloid leukemia.
 - 1. Part 1 was an open-label with 17 patients receiving eltrombopag and 11 patients completing treatment. Primary endpoint was number of participants with platelet response up to week 8 and four experienced significantly increased platelet counts, and ten had reduced platelet transfusion requirements.
 - 2. Part 2 was a randomized, double-blind with 145 patients who received supportive care plus eltrombopag (n=98) or placebo (n=47). Primary outcome was clinically relevant thrombocytopenic events (CRTE) from week 5 up to week 12. Average weekly CRTE were significantly lower with eltrombopag (54% [95% CI 43-64]) than with placebo (69% [57-80], odds ratio [OR] 0.20, 95% CI 0.05-0.87; p=0.032) although the difference between treatment groups was less than 30%. Serious adverse events were reported in 56 (58%) eltrombopag-treated patients and 32 (68%) placebo-treated patients. Seven eltrombopag recipients and two placebo recipients had serious adverse events that were suspected to be study drug-related (acute kidney injury, arterial thrombosis, bone pain, diarrhea, myocardial infarction, pyrexia, retinal vein occlusion, n=1 each; placebo: vomiting, white blood cell count increased, n=1 each). Two eltrombopag recipients had arterial thrombosis n=1 and myocardial infarction n=1. No placebo recipients experienced fatal or serious adverse events suspected to be study drug related.
 - 3. Part 3 is an extension ongoing study.
 - 4. Overall the clinical trial had a small patient population, showed limited efficacy and had questionable safety.
 - ii. Safety and tolerability of eltrombopag versus placebo for treatment of thrombocytopenia in patients with advanced myelodysplastic syndromes or acute myeloid leukemia was completed in a multicenter, randomized, placebo-controlled, double-blind, phase 1/2 trial.
 - 1. Primary outcome was safety and tolerability parameters including non-hematological laboratory Grade 3/Grade 4 toxicities, change in bone marrow blast counts from baseline, and adverse events reporting. [Time Frame: Approximately 46 months].
 - 2. Ninety-eight patients were randomized to receive either eltrombopag (n=64) or placebo (n=34). Sixty-three (98%) patients in the eltrombopag

group and 32 (94%) patients in the placebo group had adverse events. The most common adverse events were pyrexia (27 [42%] vs 11 [32%]), nausea (20 [31%] vs 7 [21%]), diarrhea (19 [30%] vs 6 [18%]), fatigue (16 [25%] vs 6 [18%]), decreased appetite (15 [23%] vs 5 [15%]), and pneumonia (14 [22%] vs 8 [24%]). Drug-related adverse events of grade 3 or higher were reported in six (9%) patients in the eltrombopag group and four (12%) patients in the placebo group.

3. In this clinical trial efficacy was not assessed.

- F. There is limited or no published clinical trial data to support the use of eltrombopag olamine (Promacta) and eltrombopag choline (Alvaiz) in conditions other than severe aplastic anemia, chronic thrombocytopenia due to chronic hepatitis C, and chronic immune thrombocytopenia (ITP).

III. Lusutrombopag (Mulpleta)

- A. There is limited or no published clinical trial data to support the use of lusutrombopag (Mulpleta) in conditions other than thrombocytopenia associated with chronic liver disease prior to a planned procedure.

IV. Fostamatinib (Tavalisse)

A. Malignancies

- i. Advanced colorectal, non-small cell lung, head, and neck, hepatocellular and renal cell carcinomas, pheochromocytoma, and thyroid tumors
 1. A broad, multi-histology, single group assignment, open label, phase II study of the multi-kinase inhibitor R935788 (fostamatinib disodium) in advanced colorectal, non-small cell lung, head and neck, hepatocellular and renal cell carcinomas, pheochromocytoma, and thyroid tumors in 37 participants.
 2. Fostamatinib had limited anti-tumor activity in this first clinical trial in patients with advanced refractory solid tumors; reduction in CECs and CEPs was indicative of anti-angiogenic effects. Abnormal liver testing at baseline appeared to influence drug tolerability.

B. B-cell Lymphoma

- i. A Phase I/II, multi-Center, single group assignment, open label trial of the safety and efficacy of fostamatinib in 81 patients with relapsed/refractory B-cell lymphoma. The clinical trial showed limited efficacy and considering it is an open label, single group trial, further clinical research is necessary to show efficacy and safety.

C. Large B-cell lymphoma, relapsed or refractory

- i. Phase II, single group assignment, open label trial with 101 participants to evaluate the efficacy of fostamatinib in patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL). The clinical trial showed limited efficacy and considering it is an open label, single group trial, further clinical research is necessary to show efficacy and safety.

D. Ovarian cancer

- i. Phase I, single group assignment, open label clinical trial of combined fostamatinib and paclitaxel in ovarian cancer with 18 participants and still recruiting.

- E. T-cell lymphoma
 - i. Phase II, multicenter, open label, single assessment group, Simon two-stage study of fostamatinib disodium in patients with relapsed or refractory T-cell lymphoma in 18 participants. The clinical trial was not blinded or randomized. It wasn't powered enough to show efficacy or safety of fostamatinib (Tavalisse) in T-cell lymphoma.
- F. Rheumatoid arthritis (RA)
 - i. A Long-term, open label, single assignment study to assess the safety of fostamatinib in the treatment of rheumatoid arthritis in Asia was terminated.
 - ii. A Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study of two dosing regimens of fostamatinib in patients with rheumatoid arthritis with an inadequate response to a tumor necrosis factor- α antagonist.
 - iii. Adult patients were randomized (1:1:1) to fostamatinib [100 mg bid for 24 weeks (n=105; Group A)], or 100 mg bid for 4 weeks, then 150 mg qd (n=108; Group B), or to placebo (n=110; Group C) for 24 weeks. Nonresponders at Week 12 could enter a long-term extension study. The primary endpoint was the proportion of patients achieving an American College of Rheumatology 20% (ACR20) response at Week 24.
 - iv. Due to efficacy and safety results from the clinical trial, the companies developing fostamatinib have decided not to study it further in RA at this time.
- G. Renal Transplant Rejection (antibody mediated rejection)
 - i. Fostamatinib is being studied in a phase 2, single center, not randomized, open label, pilot study to assess the safety and efficacy of fostamatinib in the treatment of chronic active antibody mediated rejection in renal transplantation is still recruiting.
- H. Chronic Graft vs. Host Disease
 - i. A phase I, open label, single group assignment trial of fostamatinib and chronic graft vs. host disease development after allogeneic stem cell transplantation with 18 participants is still recruiting.
- I. There is limited or no published clinical trial data to support the use of fostamatinib (Tavalisse) in conditions other than chronic immune thrombocytopenia (ITP).

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Policy Implementation/Update

Action and Summary of Changes	Date
Updated policy name to "Thrombopoietic Agents" policy. Updated initial and renewal policy criteria to include trial of generic eltrombopag olamine or eltrombopag choline (Alvaiz) prior to brand Promacta.	06/2025
Added coverage of persistent immune thrombocytopenia for eltrombopag olamine (Promacta). Removed requirement to trial oral Promacta tablets prior to Promacta packets.	05/2024
Added eltrombopag choline (Alvaiz) for the treatment of persistent or chronic immune thrombocytopenia in adult and pediatric patients 6 years of age and older, chronic Hepatitis C-associated thrombocytopenia, and severe aplastic anemia (refractory). Updated supporting evidence, references, and formatting.	03/2024
Added new strength of 25mg eltrombopag (Promacta) packet for oral suspension	05/2020
- Added investigational indications for avatrombopag (Doptelet), eltrombopag (Promacta), lusutrombopag (Mulpleta) - Added age limits to eltrombopag (Promacta) for immunosuppressive naive Severe aplastic anemia at two years of age or older, and relapsed or refractory severe aplastic anemia at 18 years of age or older. - Added criteria for Severe aplastic anemia; [Member has to meet at least two of the following three criteria are met: 1) Absolute neutrophil count (ANC) less than 500/microL, or 2) Platelet count less than 20,000/microL, or 3) Absolute reticulocyte count (ARC) less than 60,000/microL - Added member is 18 years of age or older if request is for avatrombopag (Doptelet), fostamatinib (Tavalisse) and fostamatinib (Tavalisse) [for chronic ITP] - Added criteria if request is for eltrombopag (Promacta) packets, member has demonstrated inability to swallow tablets - Changed QL for eltrombopag (Promacta) packets - Changed QL for avatrombopag (Doptelet) for chronic immune thrombocytopenia (ITP) - Changed initial and renewal length of authorization for all agents - Combined as one policy: avatrombopag (Doptelet), eltrombopag (Promacta), lusutrombopag (Mulpleta) with fostamatinib (Tavalisse)	02/2020
Previous reviews fostamatinib (Tavalisse)	06/2018, 11/2019,
Conversion to policy format fostamatinib (Tavalisse)	11/2019
Avatrombopag (Doptelet), eltrombopag (Promacta), lusutrombopag (Mulpleta) combined as policy: TPO-Receptor Agonists	10/2019
Previous reviews avatrombopag (Doptelet), eltrombopag (Promacta), lusutrombopag (Mulpleta)	10/2019,
Policy created avatrombopag (Doptelet), eltrombopag (Promacta), lusutrombopag (Mulpleta)	10/2019
Policy created fostamatinib (Tavalisse)	06/2018

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP158

Description

Tiopronin (Thiola) is an active reducing agent which undergoes thiol-disulfide exchange with cystine to form tiopronin-cystine disulfide, which is more water soluble than cystine. As a result, the amount of sparingly soluble cystine in the urine is decreased and the formation of cystine calculi is reduced.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
tiopronin (Thiola)	100 mg tablet	Nephrolithiasis (cystine), prevention	450 tablets/30 days
tiopronin (Thiola EC)	100 mg delayed release tablet		450 tablets/30 days
	300 mg delayed release tablet		150 tablets/30 days
generic tiopronin DR	100 mg delayed release tablet		450 tablets/30 days
	300 mg delayed release tablet		150 tablets/30 days

Initial Evaluation

- I. **Tiopronin (Thiola; Thiola EC)** may be considered medically necessary when the following criteria below are met:
 - A. Member is 18 years of age or older; **OR**
 1. Younger than 18 years of age and weighing 20 kg or greater; **AND**
 - B. Medication is prescribed by, or in consultation with, a nephrologist or urologist; **AND**
 - C. If the request is for brand tiopronin (Thiola EC), treatment with generic tiopronin DR has been ineffective, not tolerated, or is contraindicated; **AND**
 - D. A diagnosis of **severe homozygous cystinuria** when the following are met:
 1. Urinary cystine levels greater than 500 mg/day; **AND**
 2. Member has not been responsive to all of the following:
 - i. High fluid intake
 - ii. Urinary alkalinization
 - iii. Diet modification (e.g. restriction of sodium and protein intake)
- II. Tiopronin (Thiola; Thiola EC) is considered investigational when used for all other conditions.

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**

- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Member has exhibited improvement or stability of disease symptoms as indicated by a reduction in cystine stone production OR a urinary cystine concentration less than 250 mg/L.

Supporting Evidence

- I. Tiopronin (Thiola; Thiola EC) is a reducing-agent that helps form tiopronin-cystine disulfide, which is more readily excreted by the body, as it is more water soluble.
- II. Topronin (Thiola; Thiola EC) is FDA-approved to prevent cystine stone formation in adults and pediatric patients 20 kg and greater with severe homozygous cystinuria, who are unresponsive to high fluid intake, alkali, and diet modification.
- III. The recommended initial dose in adult patients is 800 mg/day. In clinical studies, the average dose was about 1,000 mg/day.
- IV. The recommended initial dose in pediatric patients 20 kg and greater is 15 mg/kg/day. Doses greater than 50 mg/kg per day should be avoided in pediatric patients. Pediatric patients receiving greater than 50 mg/kg tiopronin per day are at greater risk of proteinuria and nephrotic syndrome.
- V. Tiopronin (Thiola; Thiola EC) tablets are not approved for use in pediatric patients weighing less than 20 kg as safety and efficacy has not been established in this population.
- VI. Urinary cystine levels should be measured one month after initiation of tiopronin (Thiola; Thiola EC) and every three months thereafter. The dose should be adjusted to maintain a urinary cystine concentration of less than 250 mg/L.

Investigational or Not Medically Necessary Uses

- I. Tiopronin (Thiola; Thiola EC) has not been sufficiently evaluated outside of severe homozygous cystinuria.

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Added generic tiopronin to policy and required step through generic tiopronin prior to brand use	03/2024
Policy Created	12/2019

Policy Type: PA

Pharmacy Coverage Policy: UMP229

Description

Tirbanibulin (Klisyri) is a topical microtubule inhibitor.

Length of Authorization

- Initial: One-time fill
- Renewal: Not eligible/Cannot be renewed

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
tirbanibulin (Klisyri)	2.5 mg/250 mg (1%) ointment in a single-dose packet	actinic keratosis (AK)	5 packets/5 days

Initial Evaluation

- I. Tirbanibulin (Klisyri) may be considered medically necessary when the following criteria are met:
 - A. Member is 18 years of age or older; **AND**
 - B. Medication is prescribed by, or in consultation with, a dermatologist; **AND**
 - C. Member has not been treated with tirbanibulin (Klisyri) before; **AND**
 - D. A diagnosis of **actinic keratosis (AK)** when the following are met:
 1. Member will treat lesions on the face or scalp; **AND**
 2. Treatment with at least **TWO** of the following have been ineffective, not tolerated, or all are contraindicated:
 - i. 5-fluorouracil (5-FU) cream
 - ii. Imiquimod cream
 - iii. Diclofenac gel
- II. Tirbanibulin (Klisyri) is considered investigational when used for all other conditions, including but not limited to:
 - A. Patients with recurrent AK previously treated with tirbanibulin (Klisyri)
 - B. Treatment of AK on other body parts (e.g. hands, legs, neck, etc.) other than the face or scalp

Supporting Evidence

- I. The safety and efficacy of tirbanibulin (Klisyri) has been studied in adult patients, with no clinical trial data to support the use in pediatric patients; however, AK is a skin condition generally seen in the older population.
- II. AK is the most common precancer that forms on skin damaged by chronic exposure to ultraviolet (UV) rays from the sun or indoor tanning. Most AKs do not progress to squamous cell

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carcinoma (SCC), but majority of cutaneous SCCs progress from AKs. Given AK may progress to SCC, dermatologist involvement in the patient's care is recommended.

- III. Patients previously treated with tirbanibulin (Klisyri) were excluded from the clinical trials. The patients in the clinical trial only received one five-day treatment of tirbanibulin (Klisyri). The safety and efficacy of treating with a second application (i.e., treating AK that has recurred after treatment with tirbanibulin [Klisyri]) is unknown.
- IV. The safety and efficacy of tirbanibulin (Klisyri) was studied in two identically designed Phase 3, double-blind, vehicle-controlled, randomized, parallel-group, multicenter studies in 702 patients with AK of the face or scalp.
 - The majority of patients were white and male, with a Fitzpatrick skin type of I (pale white skin, blue/green eyes, blond/red hair) or II (fair skin, blue eyes) and a median of six lesions.
 - The primary efficacy outcome was complete response rate and the main secondary outcome was partial response.

Outcomes	Trial 1 (N=351)		Trial 2 (N=351)		Pooled data (N=702)	
	tirbanibulin (N=175)	vehicle (N=176)	tirbanibulin (N=178)	vehicle (N=173)	tirbanibulin (N=353)	vehicle (N=349)
Complete response rate*	77 (44%)	8 (5%)	97 (54%)	22 (13%)	174 (49%)	30 (9%)
Difference	40% 95% CI (32-47); p <0.001		42% 95% CI (33-51); p <0.001		41% 95% CI (35-47); p <0.001	
Partial Response rate**	119 (68%)	29 (16%)	136 (76%)	34 (20%)	255 (72%)	63 (18%)
Difference	52% 95% CI (43-60); p <0.001		57% 95% CI (48-65); p <0.001		54% 95% CI (48-60); p <0.0001	

* Proportion of subjects achieving complete clearance of all AK in the selected area

** Proportion of subjects achieving reduction of at least 75% in the number of lesions within the application area

- Tirbanibulin (Klisyri) treated patients who achieved CR (N=174) were included in a one year follow up; of those, 124 (73%) patients developed lesions within the area treated with tirbanibulin (Klisyri). Out of the 124 patents, 72 (58%) had recurrent lesions and 52 (42%) had new lesions. The sustained complete clearance is 27%.
 - The most common local reactions were erythema (91% of the patients) and flaking or scaling (82%). Although generally mild, crusting, swelling, vesiculation or pustulation, erosion, and ulceration were also seen.
- V. Longstanding therapies for the treatment of AK include destructive therapies [e.g., surgery, cryotherapy, dermabrasion, photodynamic therapy (PDT)], field ablation treatments (e.g., chemical peels, laser resurfacing), and topical medications (e.g., fluorouracil, imiquimod, diclofenac).
 - Topical medications including fluorouracil, imiquimod and diclofenac are used as first-line therapy with a well-established long-term efficacy and safety profile.
 - In a randomized controlled trial comparing the recurrence of AKs after treatment with fluorouracil 5%, imiquimod 5%, or PDT, fluorouracil had the highest cumulative probability of remaining free from treatment failure (defined as <75% reduction in AK lesions) 12 months after treatment. For fluorouracil, 75% of patients were free from treatment failure, followed by imiquimod at 54%, PDT at 38%.
 - Tirbanibulin (Klisyri) is a topical ointment applied once daily for five consecutive days. Patients who were previously treated with tirbanibulin (Klisyri) were excluded from the clinical trials. The patients in the clinical trial only received one five-day treatment cycle

of tirbanibulin (Klisyri) and had a high recurrence rate (73%) one year after treatment. There is limited data on long-term safety and efficacy.

Investigational or Not Medically Necessary Uses

- I. Tirbanibulin (Klisyri) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Patients previously treated with tirbanibulin (Klisyri): Patients previously treated with tirbanibulin (Klisyri) were excluded from the clinical trials. The patients in the clinical trial only received one five-day treatment cycle of tirbanibulin (Klisyri). The safety and efficacy of treating more than one 25cm² area at a time or as a second application in an area with recurrence is unknown. There is no clinical trial data to support the use in patients previously treated.
 - B. Treatment of AK on other body parts (e.g. hands, legs, neck, etc.) other than the face or scalp: The safety and efficacy of tirbanibulin (Klisyri) was studied in patients with AK of the face or scalp. No patients with lesions on other body parts were included in the clinical trial. There is no clinical trial data to support the use on other parts of the body.

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Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2021

Policy Type: PA

Pharmacy Coverage Policy: UMP313

Description

Tirzepatide (Zepbound, Mounjaro) is a glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 agonist.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
tirzepatide (Zepbound) auto-injector	Chronic weight management* Obstructive sleep apnea in adults with obesity	2.5 mg/0.5 mL	2 mL/ 28 days
		5 mg/0.5 mL	
		7.5 mg/0.5 mL	
		10 mg/0.5 mL	
		12.5 mg/0.5 mL	
tirzepatide (Zepbound) vial injection	Chronic weight management* Obstructive sleep apnea in adults with obesity	2.5 mg/0.5 mL	2 mL/ 28 days
		5 mg/0.5 mL	
tirzepatide (Mounjaro) auto-injector	Type 2 diabetes mellitus	2.5 mg/0.5 mL	2 mL/ 28 days
		5 mg/0.5 mL	
		7.5 mg/0.5 mL	
		10 mg/0.5 mL	
		12.5 mg/0.5 mL	
tirzepatide (Mounjaro) auto-injector	Type 2 diabetes mellitus	2.5 mg/0.5 mL	2 mL/ 28 days
		5 mg/0.5 mL	

*Treatment for weight loss falls in a category of medications that are not covered under the prescription benefit. Drugs used for weight loss are excluded from coverage. Please refer to the member handbook/certificate of coverage for further information.

Initial Evaluation

- Tirzepatide (Zepbound)** may be considered medically necessary when the following criteria are met:
 - Member is 18 years of age or older; **AND**
 - The request is for treatment of **Obstructive Sleep Apnea (OSA)**; **AND**
 - Documentation of moderate to severe disease defined an apnea-hypopnea index (AHI) or obstructive respiratory disturbance index (RDI) ≥ 15 without the use of a positive airway pressure device (PAP); **AND**
 - Member is currently using and will continue to use primary OSA therapy (e.g. CPAP, mandibular advancement device, etc) in combination with **tirzepatide**; **OR**

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1. Provider attestation that the member was unable to tolerate or refused primary OSA therapy (e.g. CPAP, mandibular advancement device, etc) despite proper education and adjustments; **AND**
 - E. Documentation that the member's body mass index (BMI) ≥ 30 kg/m² within the last three months; **AND**
 - F. Provider attestation that medication is used in combination with a reduced calorie diet and increased physical activity; **AND**
 - G. Tirzepatide will not be used in combination with another GLP-1 agonist
- II. **Tirzepatide (Mounjaro)** may be considered medically necessary when the following criteria are met:
- A. The member has a diagnosis of Type 2 Diabetes Mellitus AND Obstructive Sleep Apnea (OSA); **AND**
 1. Criteria I(A)-I(G) above are met; **OR**
 2. Treatment with all of the following have been ineffective, contraindicated, or not tolerated
 - i. semaglutide (Ozempic, Rybelsus)
 - ii. dulaglutide (Trulicity)
 - iii. liraglutide
 - iv. empagliflozin (Jardiance) or empagliflozin and metformin (Synjardy/Synjardy XR)
 - v. dapagliflozin (Farxiga) or dapagliflozin and metformin (Xigduo/Xigduo XR);**OR**
 - B. The request is for treatment of **Type 2 Diabetes Mellitus**; **AND**
 1. Treatment with all of the following has been ineffective, contraindicated, or not tolerated
 - i. semaglutide (Ozempic, Rybelsus)
 - ii. dulaglutide (Trulicity)
 - iii. liraglutide
 - iv. empagliflozin (Jardiance) or empagliflozin and metformin (Synjardy/Synjardy XR)
 - v. dapagliflozin (Farxiga) or dapagliflozin and metformin (Xigduo/Xigduo XR)
- III. Tirzepatide (Zepbound) is considered investigational when used for all other conditions, including but not limited to:
- A. Obstructive sleep apnea (OSA) in patients without obesity

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**

- III. Member has exhibited improvement or stability of disease symptoms [e.g., improved A1c, improved AHI, reduction in excessive daytime sleepiness, improved sleep-related quality of life, etc); **AND**
- IV. The request is for **tirzepatide (Zepbound)**; **AND**
 - A. Member will continue to use primary obstructive sleep apnea (OSA) therapy (e.g. CPAP, mandibular advancement device, etc) in combination with **tirzepatide**; **OR**
 - 1. Provider attestation that the member was unable to tolerate or refused primary OSA therapy (e.g. CPAP, mandibular advancement device, etc) despite proper education and adjustments; **AND**
 - B. Provider attestation that medication is used in combination with a reduced calorie diet and increased physical activity; **AND**
 - C. Documentation that the member's body mass index (BMI) ≥ 30 kg/m² within the last three months; **AND**
 - D. Tirzepatide will not be used in combination with another GLP-1 agonist; **OR**
- V. The request is for **tirzepatide (Mounjaro)**

Supporting Evidence

- I. Tirzepatide (Zepbound) was FDA for treatment of moderate to severe obstructive sleep apnea in adults with obesity on December 20, 2024. Tirzepatide (Zepbound) has not been studied in patients <18 years of age for treatment of obstructive sleep apnea (OSA) in adults with obesity, therefore, the net health benefit in a younger patient population has not been established at this time.
- II. Tirzepatide (Zepbound) in treatment of OSA in adults with obesity was studied in one Phase 3, randomized, double-blinded, placebo-controlled trial (SURMOUNT-OSA). Participants were 18 years or older, had a diagnosis of moderate-to-severe OSA, defined by an apnea-hypopnea index (AHI) ≥ 15 , and had a BMI ≥ 30 kg/m². Weight loss medications were not permitted during enrollment. The study split participants into two groups. Those that did not receive prior continuous positive airway pressure (CPAP) were placed in cohort 1 and those that did receive prior PAP were placed in cohort 2. The primary endpoint was change in AHI at week 52 and secondary endpoints included change in hypoxic burden and patient-reported sleep impairment and disturbance. At baseline, the mean AHI was 51.5 in cohort 1 and 49.5 in cohort 2, and mean BMI 39.1 and 38.7, respectively. After 52 weeks, cohort 1 had a mean change in AHI of -25.3 events with tirzepatide (95% CI, -29.3 to -21.2) and -5.3 events with placebo (95% CI, -9.4 to -1.1), $p < 0.001$. This correlates to an AHI lowering of about 50%. Cohort 2 had a mean change in AHI of -29.3 events with tirzepatide (95% CI, -33.2 to -25.4) and -5.5 events with placebo (95% CI, -9.9 to -1.2), $p < 0.001$. This correlates to an AHI lowering of about 57%.
- III. There was a significant change in sleep-apnea-specific hypoxic burden between active and placebo arms, difference of -70.1% min/hr (95% CI, -90.9 to -49.3) and -61.3% (95% CI, -84.7 to -37.9) in trials 1 and 2, respectively. The Patient-Reported Outcomes Measurement Information (PROMIS) score difference between tirzepatide and placebo were -3.9 (95% CI, -5.7 to -2.2) and -3.1 (-4.5 to -1.5) in trials 1 and 2, respectively. There is moderate to high confidence that tirzepatide (Zepbound) reduces AHI as well as AHI burden when compared to placebo in treatment of OSA.

- IV. The 2019 American Academy of Sleep Medicine Clinical Practice guideline, 2018 American Thoracic Society Clinical Practice Guideline, and Cleveland Clinic Journal of Medicine Treatments for Obstructive Sleep Apnea guidelines support the use of reduction in AHI scores and oxygen desaturation levels to support efficacy in treatment OSA.
- V. Documentation of patient's body mass index (BMI) within the last three months is required to assess medical necessity for use. The safety and efficacy of tirzepatide (Zepbound) for OSA in adults has not been established in those with BMI <30mg/kg².
- VI. The most frequently reported adverse events were generally gastrointestinal and occurred more frequently in the participants who received tirzepatide. These events were generally mild-to-moderate in severity and occurred most frequently during the dose-escalation phase. Serious adverse events were reported by 35 participants (7.5%) overall. Similar percentages of participants in the tirzepatide and placebo groups experienced adverse events. There were two confirmed cases of acute pancreatitis in the trial 2 tirzepatide group.
- VII. Participants in SURMOUNT-OSA were permitted to continue CPAP while enrolled in the study. CPAP has been shown to reduce AHI by 72.5% in patients with OSA (compared to tirzepatide's reduction in AHI of 50% as monotherapy and 57% when used in combination with CPAP). The 2019 American Academy of Sleep Medicine Clinical Practice guideline, 2018 American Thoracic Society Clinical Practice Guideline, and Cleveland Clinic Journal of Medicine Treatments for Obstructive Sleep Apnea guidelines note that CPAP is the gold standard therapy for adult patients with moderate to severe OSA. Moderate to severe OSA is defined by an AHI score of >15. Mild OSA is defined by an AHI score of 5 to 15. Guidelines note that the use of primary OSA therapy (e.g. CPAP) in this population may improve quality of life and reduce OSA-related excessive daytime sleepiness, fatigue, insomnia, uncontrolled hypertension, and heart disease.
- VIII. Weight loss interventions and lifestyle modifications may be used in addition to PAP to treat OSA. Therefore, requiring PAP in treatment of OSA is clinically appropriate. For maximum benefit, standard of care agents for OSA should be optimized.
- IX. Tirzepatide (Mounjaro) is FDA for treatment of type 2 diabetes mellitus. The 2024 ADA guidelines support the use of Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1) as options for glycemic management and categorize these medications as a "high" likelihood of achieving glycemic goals. Guidelines do not make a recommendation of one agent over the other and requiring treatment with semaglutide (Ozempic, Rybelsus), dulaglutide (Trulicity), empagliflozin (Jardiance, Synjardy/Synjardy XR), dapagliflozin (Farxiga, Xigduo/Xigduo XR), and liraglutide is clinically appropriate and cost effective.
- X. While Mounjaro and Zepbound carry different FDA-approved indications, they are both available in all the same doses and dosage forms. Mounjaro and Zepbound can deliver the right amount of tirzepatide to treat both type 2 diabetes mellitus and OSA. OSA is a common comorbidity in patients with type 2 diabetes.

Investigational or Not Medically Necessary Uses

- I. Tirzepatide (Zepbound) is considered investigational when used for all other conditions, including but not limited to:
 - A. Obstructive sleep apnea (OSA) in patients without obesity

1. The safety and efficacy of tirzepatide (Zepbound) for OSA in adults has not been established in those with BMI <30mg/kg²
- B. Metabolic dysfunction-associated steatohepatitis (MASH), or formerly nonalcoholic steatohepatitis (NASH)
- C. Heart failure with preserved ejection fraction
- D. Chronic kidney disease

References

1. Zepbound (tirzepatide) [prescribing information]. Indianapolis, IN: Lilly USA LLC; December 2024.
2. Malhotra A, Bednarik J, Chakladar S, et al. Tirzepatide for the treatment of obstructive sleep apnea: Rationale, design, and sample baseline characteristics of the SURMOUNT -OSA phase 3 trial. *Contemp Clin Trials*. 2024;141:107516.
3. Aboussouan LS, Bhat A, Coy T, Kominsky A. Treatments for obstructive sleep apnea: CPAP and beyond. *Cleve Clin J Med*. 2023;90(12):755-765. Published 2023 Dec 1.
4. Hudegel DW, Patel SR, Ahasic AM, et al. The Role of Weight Management in the Treatment of Adult Obstructive Sleep Apnea. An Official American Thoracic Society Clinical Practice Guideline. *Am J Respir Crit Care Med*. 2018;198(6):e70-e87.
5. Patil SP, Ayappa IA, Caples SM, Kimoff RJ, Patel SR, Harrod CG. Treatment of adult obstructive sleep apnea with positive airway pressure: an American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med*. 2019;15(2):335-343.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
Semaglutide (Wegovy®)	Major adverse cardiovascular events (MACE) risk reduction in adults with established cardiovascular disease and obesity or overweight Excess body weight and weight maintenance in patients 12 years and older with obesity and adults with overweight
Medications for Weight Management	Chronic weight management in pediatric patients

Policy Implementation/Update:

Action and Summary of Changes	Date
Removed criteria requiring trial of T2DM medications for members with OSA+T2DM. Added criteria II.A.2 and reworded renewal criteria to improve flow.	08/2025
Rearranged and reworded criteria to improve flow	06/2025
Mounjaro updated to require prior authorization. Criteria added to support medical necessity review for Type 2 Diabetes Mellitus. Removed specialist requirement. Updated criteria for moderate to severe OSA and language around trial of primary OSA therapy. Access limited moderate to severe disease defined by an apnea-hypopnea index (AHI) or obstructive respiratory disturbance index (RDI) ≥15.	05/2025
Live 1/1/2025 - New Policy	11/2024

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP230

Description

Tivozanib (Fotivda) is an orally administered VEGFR kinase inhibitor.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
tivozanib (Fotivda)	1.34 mg capsules	Relapsed or refractory advanced renal cell carcinoma, following at least two prior systemic therapies	21 capsules/28 days
	0.89 mg capsules		

Initial Evaluation

- I. **Tivozanib (Fotivda)** may be considered medically necessary when the following criteria are met:
 - A. Member is 18 years of age or older; **AND**
 - B. Medication is prescribed by, or in consultation with, an oncologist; **AND**
 - C. Not used in combination with any other oncology therapy (e.g., everolimus [Afinitor], temsirolimus (Torisel), ipilimumab [Yervoy], nivolumab [Opdivo]; **AND**
 - D. A diagnosis of **advanced or metastatic renal cell carcinoma** when the following are met:
 1. Provider attestation the member has clear cell component histology; **AND**
 2. Member has renal cell carcinoma that is relapsed or refractory to at least **TWO** prior systemic therapies (e.g., axitinib [Inlyta], ipilimumab [Yervoy], nivolumab [Opdivo], everolimus [Afinitor]; **AND**
 - i. At least **ONE** of the prior therapies is an anti-VEGFR TKI (e.g., axitinib [Inlyta], lenvatinib [Lenvima], pazopanib [Votrient], sunitinib [Sutent], cabozantinib [Cabometyx]).
- II. Tivozanib (Fotivda) is considered not medically necessary when criteria above are not met and/or when used for:
 - A. Renal cell carcinoma prior to third-line treatment
- III. Tivozanib (Fotivda) is considered investigational when used for all other conditions, including but not limited to:
 - A. Renal cell carcinoma in combination with other oncolytic therapies

- B. Renal cell carcinoma prior to the relapsed refractory and/or advanced settings
- C. Prostate cancer
- D. Breast cancer
- E. Ovarian, fallopian tube, or primary peritoneal cancer
- F. Lung Cancer
- G. Gastrointestinal tumors
- H. Hepatocellular carcinoma
- I. Cholangiocarcinoma
- J. Colorectal cancer
- K. Glioblastoma

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Provider attestation the medication will not be used in combination with any other oncology therapy (e.g., everolimus [Afinitor], temsirolimus (Torisel), ipilimumab [Yervoy], nivolumab [Opdivo]; **AND**
- IV. Disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread.

Supporting Evidence

- I. Tivozanib (Fotivda) is a VEGFR tyrosine kinase inhibitor (TKI) that is FDA-approved for patients with relapsed or refractory advanced renal cell carcinoma (RCC) following two or more systemic therapies. Tivozanib (Fotivda) is approved for 21 days on therapy and seven days off until disease progression or unacceptable toxicity. It is the first therapy specifically FDA-approved for the third-line setting, but joins several other anti-VEGFR medications for this condition, as well as immunotherapies and mTOR inhibitors. All therapy categories are utilized in the subsequent treatment setting after members have progressive disease.
- II. Other anti-VEGFR medications include: cabozantinib (Cabometyx), pazopanib (Votrient), sorafenib (Nexavar), lenvatinib (Lenvima), sunitinib (Sutent) and axitinib (Inlyta). Immunotherapy options include: ipilimumab (Yervoy), nivolumab (Opdivo), avelumab (Bavencio). The mTOR inhibitors include therapies such as everolimus (Afinitor), temsirolimus (Torisel). Often, immunotherapies will be used in combination with each other, or in combination with anti-VEGFR medications. The mTOR inhibitors are also utilized in combination with anti-VEGFR medications; however, use of two concomitant anti-VEGFR medications has not been evaluated, and given the unfavorable safety profiles of these medications, combination treatment is not advised.
- III. As of March 2021, all three categories of medications are used for clear cell RCC. In the subsequent treatment setting, NCCN Cat. 1 recommended regimens include cabozantinib

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(Cabometyx), nivolumab (Opdivo), axitinib (Inlyta), and lenvatinib (Lenvima) plus everolimus (Afinitor). The remainder have Cat. 2A recommendations, with the exception of sorafenib (Nexavar) which has a Cat. 2B recommendation.

- IV. Treatment choice is based on stage of disease, prognosis, line of therapy, and other patient characteristics. Tolerability and safety considerations are taken into account for treatment choice as well. Given the extensive treatment options, combinations, and unfavorable safety profiles that require extensive medication monitoring, medication should be prescribed by or in consultation with a specialist.
- V. In 2013 tivozanib (Fotivda) was evaluated in a Phase 3 trial vs. sorafenib (Nexavar) in 517 patients with RCC for initial targeted therapy in those that had received up to one prior systemic treatment. Patients had prior nephrectomy, clear cell RCC, and up to one prior therapy that was not an anti-VEGFR. Progression-free survival (PFS) was statistically significant favoring tivozanib (Fotivda); however, the overall survival (OS) was not statistically different. In 2013, the FDA issued a Complete Response Letter to Aveo, given an inconclusive risk benefit assessment and required another trial from the manufacturer in the advanced setting.
- VI. Following the CRL, tivozanib (Fotivda) was evaluated in an open-label, randomized, Phase 3 trial vs. sorafenib (Nexavar) in 350 adults with RCC. Ninety-eight percent of patients had clear cell histology. Patients had advanced disease and were relapsed or refractory to two or three prior systemic therapies, including at least one anti-VEGFR therapy. Forty-five percent of patients had two prior anti-VEGFR therapies and 26% had prior checkpoint inhibitor therapy. About 60% of patients had intermediate, 20% had favorable, and 20% had poor prognoses. The study showed a statistical increase in PFS (5.6 months vs. 3.9 months), as well as partial responses (18% vs. 8%); however, OS was not statistically different and numerically favored sorafenib (Nexavar). To date, tivozanib (Fotivda) has not proven to have clinically meaningful outcomes such as increased survival, improvement in quality of life or symptom control. This is similar for the comparator, sorafenib (Nexavar). Thus, clinical benefit of either therapy remains unclear.
- VII. To date, the safety tivozanib (Fotivda) is similar to other anti-VEGFR medications. Serious adverse events (AE) occurred in 11% of patients on tivozanib (Fotivda) and in 10% for sorafenib (Nexavar). AE more frequent with tivozanib (Fotivda): hypertension (44% vs. 31%), bleeding (17% vs. 12%), nausea (30% vs. 18%), decreased appetite (39% vs. 30%), dysphonia (27% vs. 9%), cough (22% vs. 15%), and hypothyroidism (24% vs. 11%). AE more frequent with sorafenib (Nexavar): diarrhea (54% vs. 44%), rash (52% vs. 18%), and palmar-plantar syndrome (41% vs. 16%). Stomatitis, vomiting, pain, dyspnea, and weight loss were common and occurred in similar rates between treatment arms
- VIII. Dose interruption due to AE occurred in 48% of the tivozanib (Fotivda) group and 63% of the sorafenib (Nexavar) group. Dose reductions due to AE occurred in 24% for tivozanib (Fotivda) and 38% for sorafenib (Nexavar). The lower dose reduction and interruption rates for tivozanib (Fotivda) are likely attributable to the seven-day break within each cycle vs. continuous dosing with sorafenib (Nexavar). Given lack of long-term safety evaluation and lack of evaluation against placebo, true benefits and harms are unknown at this time. At this time there is insufficient safety information (given limited patient experience and duration of therapy) to definitively indicate that there is substantial safety differences between any of the anti-VEGFR therapies.

Investigational or Not Medically Necessary Uses

- I. Tivozanib (Fotivda) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Renal cell carcinoma prior to third-line.
 - i. Tivozanib (Fotivda) has been evaluated for first-line and second-line treatment but did not achieve FDA-approval given uncertain risks and benefits.
 - B. The following indications have not been sufficiently studied for efficacy and use outside of clinical trials is not advised given the unfavorable safety profile alone or in combination with other medications:
 - i. Renal cell carcinoma in combination with other oncolytic therapies
 - ii. Renal cell carcinoma prior to the relapsed refractory and/or advanced settings
 - iii. Prostate cancer
 - iv. Breast cancer
 - v. Ovarian, fallopian tube, or primary peritoneal cancer
 - vi. Lung Cancer
 - vii. Gastrointestinal tumors
 - viii. Hepatocellular carcinoma
 - ix. Cholangiocarcinoma
 - x. Colorectal cancer
 - xi. Glioblastoma

References

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2. Rini BI, Pal SK, Escudier BJ, et al. Tivozanib versus sorafenib in patients with advanced renal cell carcinoma (TIVO-3): a phase 3, multicentre, randomized, controlled, open-label study. *Lancet Oncol.* 2020;21(1):95-104.
3. Motzer RJ, Nosov D, Eisen T, et al. Tivozanib versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma: results from a phase III trial. *J Clin Oncol.* 2013;31(30):3791-3799.
4. NCCN Guidelines for the Treatment of Kidney Cancer. V.2.2021. Updates February 3, 2021.
5. Powles T, ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Recent eUpdate to the ESMO Clinical Practice Guidelines on renal cell carcinoma on cabozantinib and nivolumab for first-line clear cell renal cancer: Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2021;32(3):422-423

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2021

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP159

Tobramycin (TOBI®) inhalation solution, generic tobramycin inhalation solution, tobramycin (KITABIS™) inhalation solution, tobramycin (TOBI Podhaler®) inhalation solution and tobramycin (Bethkis®) inhalation solution are aminoglycoside antibacterial drugs that act primarily by disrupting protein synthesis in the bacterial cell which eventually leads to death of the cell. Tobramycin inhalation solutions have activity against a wide range of gram-negative bacteria including *Pseudomonas aeruginosa*.

Length of Authorization

- Initial:
 - i. Non-Cystic Fibrosis Chronic Bronchiectasis: 6 months (3 fills)
 - ii. Cystic Fibrosis with *Pseudomonas aeruginosa*: 12 months (7 fills per year)
- Renewal:
 - i. Non-Cystic Fibrosis Chronic Bronchiectasis: None, initial criteria applies
 - ii. Cystic Fibrosis with *Pseudomonas aeruginosa*: 12 months (7 fills per year)

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
tobramycin (TOBI)	Cystic fibrosis with <i>Pseudomonas aeruginosa</i>	300 mg/5mL one single-use ampule	56 single-dose ampules/28 days
generic tobramycin inhalation solution		300 mg/5mL one single-use ampule	56 single-dose ampules/28 days
tobramycin (KITABIS)		300 mg/5mL one single-use ampule	56 single-dose ampules/28 days
tobramycin (Bethkis)	Non- cystic fibrosis Chronic Bronchiectasis	300 mg/4 mL one single-use ampule	56 single-dose ampules/28 days
tobramycin (TOBI Podhaler)		28mg inhalation capsule	224 inhalation capsules /28 days

Initial Evaluation

- I. **Generic tobramycin inhalation solution** may be considered medically necessary when the following criteria below are met:
 - A. Member is six years of age or older for a diagnosis of cystic fibrosis; **OR**
 1. Member is 18 years of age or older for a diagnosis of chronic bronchiectasis; **AND**
 - B. Medication is prescribed by, or in consultation with, a pulmonologist; **AND**
 - C. A diagnosis of **cystic fibrosis** when the following are met:
 1. Member has tested positive for *Pseudomonas aeruginosa* in the lungs; **AND**
 2. Member has a documented baseline FEV₁ percentage (this may be used in renewal at a later date); **AND**
 3. Member is not colonized with *Burkholderia cepacia*; **OR**
 - D. A diagnosis of **chronic bronchiectasis** when the following are met:

1. Member has tested positive for *Pseudomonas aeruginosa* in an airway culture (e.g., lungs, sputum, nasopharyngeal) for initial treatment OR re-infection; **AND**
 2. Member has had at least two exacerbations in the last 12 months that have required acute antibiotic treatment (10-14 days in length); **AND**
 3. Member has failed long-term oral antibiotic treatment (e.g., ciprofloxacin, levofloxacin, moxifloxacin, azithromycin, sulfamethoxazole/trimethoprim)
- II. **Tobramycin (TOBI) inhalation solution, tobramycin (KITABIS) inhalation solution, tobramycin (BETHKIS) inhalation solution and tobramycin (TOBI Podhaler) inhalation solution** may be considered medically necessary when the following criteria below are met:
- A. Criteria I(A)-I(D) above are met; **AND**
 - B. Treatment with generic tobramycin inhalation solution has been ineffective, contraindicated, or not tolerated.
- III. Generic tobramycin inhalation solution, tobramycin (KITABIS) inhalation solution, tobramycin (TOBI) inhalation solution, tobramycin (BETHKIS) inhalation solution and tobramycin (TOBI Podhaler) inhalation solution are considered investigational when used for all other conditions, including but not limited to:
- A. Non-cystic fibrosis chronic bronchiectasis with another bacterial culture outside of *Pseudomonas aeruginosa*

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
- II. Member has a diagnosis of Cystic Fibrosis with *Pseudomonas aeruginosa*; **AND**
- III. Member has exhibited improvement or stability of disease symptoms (i.e., stabilization or improvement of FEV1, reduced number of respiratory-related hospitalizations or reduced exacerbations).

Supporting Evidence

- I. Due to the complexity of the disease states of the policy, tobramycin inhalation solution needs to be prescribed by, or in consultation with, a pulmonologist or an infectious disease specialist.
- II. For the treatment of Cystic Fibrosis, the safety and efficacy of tobramycin inhalation solution in pediatric patients under six years of age has not been established due to the lack of clinical trial data. The use is not indicated in pediatric patients under the age of six.
 - Tobramycin inhalation solution is administered twice daily in alternating periods of 28 days to help prevent resistance to tobramycin and offset potential adverse events (ADE). After 28 days of therapy, patients should stop tobramycin therapy for the next 28 days, and then resume therapy for the next “28 days on/28 days off” cycle. To ensure appropriate dosing of tobramycin nebulizer or podhaler in members with cystic fibrosis, approval will allow for 7 fills within a one year approval period.

- Safety and efficacy have not been demonstrated in patients with FEV1 <40% or >80% (Bethkis), FEV1 <25% or >80% (Tobi Podhaler), FEV1 <25% or >75% (Tobi and Kitabis), or patients colonized with *Burkholderia cepacia*. However, real world application does suggest value in patients outside these ranges as some patients may have low FEV1 values, but still have good quality of life with regular jobs, travel, and limited oxygen use for sleep versus other patients who may have FEV1 over 40 and still require oxygen around the clock, unable to work on disability. Therefore, a documented FEV1 is required from baseline as use of tobramycin is used to maintain or improve FEV1 and renewal criteria reflects this ask.
- Guidelines developed by the Pulmonary Therapies Committee of the Cystic Fibrosis Foundation made the following recommendations for tobramycin solution for inhalation (TSI) (written prior to the approval of aztreonam lysine inhalation solution (AZLI)):
 - Moderate to severe lung disease (>6 years of age): For patients colonized with *P. aeruginosa*, the chronic use of TSI is strongly recommended to improve lung function and reduce exacerbations (grade A recommendation).
 - Mild lung disease or asymptomatic (>6 years of age): For patients colonized with *P. aeruginosa*, the chronic use of TSI is recommended to reduce exacerbations (grade B recommendation).

III. For the treatment of chronic bronchiectasis, safety and efficacy has not been established in pediatric patients, those under 18 years of age.

- Chronic infection is a hallmark in bronchiectasis; the US Bronchiectasis Research Registry reported 1826 patients with bronchiectasis with the most common organism found causing the infection to be *Pseudomonas aeruginosa* (33%). The majority of patients, with normal lung function tests (i.e., forced vital capacity, FVC), are able to clear this infection with antibiotics, while those with impaired lung function are unable to. When the patient has frequent exacerbations (three or more a year), targeted chronic antibiotic strategies may be helpful in reducing exacerbations and improving quality of life.
- The fluoroquinolone family is typically used first line for both acute and chronic bronchiectasis, macrolide use also is supported for those with allergies. Both classes have demonstrated benefit versus placebo in regard to reducing frequency of exacerbations. Chronic dosing may look like azithromycin 250mg three times a week which can be increased according to clinical response or adverse events or ciprofloxacin twice daily.
- The British Thoracic Society guidelines give the clearest step wise approach to care calling for steps one and two being treatment of underlying causes, pulmonary rehabilitation, and acute antibiotic use (mainly oral), before moving into step three where patients are having exacerbations despite prevention care. Patients are then recommended to undergo pathogen testing and recommended either long term macrolides or inhaled tobramycin, or a combination of both should patients still continue to have worsening symptoms. Intravenous (IV) antibiotics are more reserved for those patients with continued hospitalization despite all of the above.

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UpToDate also holds IV use for those acutely critically ill, or those with known antibiotic resistance.

- Inhaled antibiotics, such as tobramycin, have been used in the refractory setting, mainly in those with chronic infection of *Pseudomonas aeruginosa*. However, studies have not shown consistent benefit.
 - i. Drobnic et al. 2005: double-blind, placebo-controlled, crossover study randomized 30 patients to initial tobramycin inhaled solution (TIS) 300 mg or placebo BID for 6 months, followed by a one-month washout period and 6 months of therapy with the other treatment. During the first treatment period, TIS treatment resulted in a significant reduction in *P. aeruginosa* density compared with placebo ($P = 0.038$). During both treatment periods, patients treated with TIS had fewer hospital admissions (0.15 vs. 0.75; $P = 0.038$) and fewer days of admission (2.05 vs. 12.65; $P = 0.047$) than patients treated with placebo, respectively. No significant changes occurred with number of exacerbations and pulmonary function tests.
 - ii. Barker et al. 2000: randomized, double-blind, placebo-controlled study, patients received either TIS 300 mg ($n = 37$) or placebo ($n = 37$) twice daily for 4 weeks and were followed for an additional 2 weeks off treatment. At Week 4, the TIS group had a mean decrease in *P. aeruginosa* density of 4.54 log₁₀ colony-forming units (CFU)/g of sputum compared with no change in the placebo group ($P < 0.01$). At Week 6, complete eradication of *P. aeruginosa* occurred in 35% of the patients in the TIS group compared with none in the placebo group, and 62% of patient in the TIS group vs. 38% of the placebo group showed an improved condition. Mean percent change in FEV1 percent predicted from Week 0 to Week 4 was similar for the TIS and placebo groups ($P = 0.41$)
 - iii. Orriols et al. 2015: randomized, single-blind study, patients received TIS 300 mg ($n = 16$) or placebo ($n = 19$) BID for 3 months following a 14-day course of intravenous ceftazidime and tobramycin and were followed for an additional 12 months. Median time to recurrence of *P. aeruginosa* infection was higher in TIS group than in the placebo group ($P = 0.048$). At the end of the study 54.5% of the patients were free of *P. aeruginosa* in the tobramycin group ($n = 6/11$) and 29.4% in the placebo group ($n = 5/17$). The numbers of exacerbations (1.27 vs. 2.5; $P = 0.044$), hospital admissions (0.06 vs. 0.47; $P = 0.037$) and days of hospitalization (0.9 vs. 13.56; $P = 0.034$) were lower in the tobramycin than in the placebo group. No significant difference was found in pulmonary function tests.
 - iv. The BATTLE study was a randomized, double-blind, placebo-controlled study in the Netherlands of adult patients treated with tobramycin inhaled solution (TIS) once daily ($n=26$) or placebo daily ($n=26$) for 52 weeks with a primary outcome of a yearly rate of pulmonary exacerbations. Those in the TIS group had 41 exacerbations over the year compared to 58 in the placebo group. At the end of the study, no pathogens were in the sputum of 10 patients the TIS group versus four of the placebo group.

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- v. The iBEST study was the largest study with 107 total patients randomized 1:1:1 to receive TIS daily at three different doses (84, 140, or 224mg) and within each group the patients either received continuous TIS or cyclic TIS [28 days on/28 days off] or placebo). All patients were adults. The primary endpoint was change in *P. aeruginosa* sputum density. Each group met statistical significance versus placebo, with 224mg achieving the best change in density. Additionally, those receiving cyclic TIS versus continuous dosing schedule also achieved higher clearance, but this was only significant in the 224mg branch and not in the lower doses.
 - The society guidelines vary in their position on tobramycin in the treatment of chronic bronchiectasis. The European Respiratory Society and the British Thoracic guidelines have incorporated tobramycin into the treatment of chronic bronchiectasis, where the United States guidelines are not updated to include this. These guidelines recommend a therapeutic trial of inhaled antibiotics in patients with three or more exacerbations a year or significant morbidity from fewer exacerbations and *Pseudomonas aeruginosa* in their sputum; however, the clinical trials widely included those with only two. Our criteria reflects two so we are able to catch moderately affected patients and hopefully prevent additional hospitalizations.
 - Due to the variability of the time frames of the clinical trial, we have gone with cyclic dosing as recommended via the iBEST trial with dosing of 300mg TIS twice daily due to the highest clearance of *P. aeruginosa* in the treatment arms and the collected knowledge from the other trials that as low as one month of treatment reduced exacerbations. Additionally, there is not a clear consensus to how many months of therapy patients require, so we are allowing six months for three rounds of therapy without refills to where the patient would be required to meet initial criteria on the next occurrence. This is also to avoid undue adverse events as each clinical trial was associated with higher ADE in the TIS arms than placebo with varying discontinuation rates due to these adverse events.
 - The body of evidence overall is lacking in robustness of data. The clinical programs looking at this use were under powered or met surrogate endpoints, example eradicating *P. aeruginosa*, but did not consistently impact time to next exacerbation or increased actual lung function, and there was an increased number of adverse effects from the medication itself. There was a lower number of hospitalizations, which is a positive quality of life piece for the patients, but this is not a correlation in improvements to the disease itself.
- IV. In the absence of direct comparative trails there's no evidence to conclude that one product is safer or more effective than another.

Investigational or Not Medically Necessary Uses

- I. Non-cystic fibrosis chronic bronchiectasis for treatment of acute exacerbations OR those not colonized with *Pseudomonas aeruginosa*

References

1. KITABIS PAK [Prescribing Information] Catalent Pharma Solutions, LLC Woodstock, IL 60098. 8/2021
2. TOBI Podhaler [Prescribing Information] Novartis Pharmaceuticals Corporation 2/2023
3. TOBI inhalation solution [Prescribing Information]. Novartis Pharmaceuticals Corporation 4/2020
4. Bethkis inhalation solution [Prescribing Information]. Chiesi USA, Inc 12/2019
5. Barker, A. F. (n.d.). Treatment of bronchiectasis in adults. Retrieved from [https://www-uptodate.com.liboff.ohsu.edu/contents/treatment-of-bronchiectasis-in-adults?search=tobramycin in Non-cystic fibrosis bronchiectasis&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2#H23](https://www-uptodate.com.liboff.ohsu.edu/contents/treatment-of-bronchiectasis-in-adults?search=tobramycin%20in%20Non-cystic%20fibrosis%20bronchiectasis&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2#H23)
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10. Drobnic ME, Suñé P, Montoro JB, et al. Inhaled tobramycin in non-cystic fibrosis patients with bronchiectasis and chronic bronchial infection with Pseudomonas aeruginosa. Ann Pharmacother. 2005 Jan;39(1):39-44. doi: 10.1345/aph.1E099. Epub 2004 Nov 23. PMID: 15562142.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy

Policy Name	Disease state
Cystic Fibrosis, CFTR Modulators	Cystic Fibrosis
dornase alfa (Pulmonzyme)	
mannitol (Bronchitol)	
aztreonam (Cayston)	

Policy Implementation/Update:

Action and Summary of Changes	Date
Edited FEV1 in criterion setting of CF to remove specific values. Updates to supporting evidence. Added in criteria for coverage for non-CF bronchiectasis per request of UMP as well as updated supporting evidence for this addition. Formatting updates.	06/2023
Removed step through tobramycin (BETHKIS) inhalation solution and tobramycin (KITABIS) inhalation solution	12/2021
- Updated criteria to policy format - Tobramycin (TOBI Podhaler) inhalation solution is considered medically necessary if treatment with tobramycin (KITABIS) inhalation solution and tobramycin (TOBI) inhalation solution has been ineffective, contraindicated, or not tolerated - Tobramycin (TOBI) inhalation solution and tobramycin (BETHKIS) inhalation solution are considered medically necessary if treatment with tobramycin (KITABIS) and generic tobramycin has been ineffective, contraindicated or not tolerated - Added tobramycin (KITABIS) to policy	12/2019
Previous Reviews	03/2013; 03/2017;

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP068

Description

Tolvaptan (Jynarque) is a selective vasopressin V(2)-receptor antagonist.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
tolvaptan (generic and brand Jynarque)	Autosomal dominant polycystic kidney disease	15 mg tablets	28 tablets/28 days
		30 mg tablets	60 tablets/30 days
		15 & 15 mg tablet therapy pack	56 tablets/28 days (1 box/28 day)
		30 & 15 mg tablet therapy pack	56 tablets/28 days (1 box/28 day)
		45 & 15 mg tablet therapy pack	56 tablets/28 days (1 box/28 day)
		60 & 30 mg tablet therapy pack	56 tablets/28 days (1 box/28 day)
		90 & 30 mg tablet therapy pack	56 tablets/28 days (1 box/28 day)

Initial Evaluation

- I. **Tolvaptan (Jynarque)** may be considered medically necessary when the following are met:
 - A. Prescribed by prescribed by, or, in consultation with a nephrologist; **AND**
 - B. A diagnosis of **autosomal dominant polycystic kidney disease (ADPKD)** when the following are met:
 1. Member is at risk of rapidly progressing ADPKD (e.g., reduced or declining renal function, high or increasing total kidney volume [height adjusted]); **AND**
 2. Member does not have Stage 5 chronic kidney disease (CKD) defined as a glomerular filtration rate {GFR} < 15 mL/min/1.73 m², or receiving dialysis; **AND**
 - C. The request is for brand Jynarque (tolvaptan); **OR**
 1. The request is for generic tolvaptan; **AND**
 - i. Treatment with brand Jynarque (tolvaptan) has been ineffective, not tolerated, or is contraindicated
- II. Tolvaptan (Jynarque) is considered investigational when used for all other conditions, including but not limited to:
 - A. Hyponatremia

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Member experienced disease stability, or improvement (e.g., reduction in number and/or rate of cyst production, change in renal function, reduction in rate of total kidney volume growth, slowed rate of kidney function decline)

Supporting Evidence

- I. Polycystic kidney disease (PKD) includes inherited diseases that cause irreversible decline in kidney function. PKD may be inherited as an autosomal dominant or recessive trait. The autosomal dominant form (autosomal dominant PKD [ADPKD]) is the most common genetic cause of chronic kidney disease (CKD). The majority of individuals with PKD eventually require renal replacement therapy.
- II. The diagnosis of ADPKD is most commonly made via screening using ultrasound, CT scan or MRI. Genetic testing is available for definitive diagnosis but is rarely performed. Confirmed diagnosis of ADPKD via one of these tests is required prior to coverage of Jynarque.
- III. Tolvaptan (Jynarque) was shown to slow the rate of decline in renal function in adults at risk of rapidly progressing ADPKD in two phase 3 randomized controlled trials, TEMPO and REPRISE.
 - TEMPO: Included 1445 adult patients with estimated creatinine clearance >60 mL/min and total kidney volume (TKV) >750 mL. The trial met the pre-specified primary endpoint of 3-year change in TKV ($p < 0.0001$). The annual decline in eGFR was slower among patients who received tolvaptan compared to placebo (-2.72 versus -3.70 mL/min/1.73 m² per year). Tolvaptan also reduced the rate of decline in kidney function at three years (hazard ratio [HR] 0.39, 95% CI 0.26-0.57), and the incidence of clinically significant kidney pain (HR 0.64, 95% CI 0.47-0.89).
 - REPRISE: Examined the effect of tolvaptan in patients with ADPKD who had reduced eGFR; such patients were generally not included in the TEMPO trial. At 12 months, the change from baseline eGFR was lower among those assigned tolvaptan as compared with placebo (-2.34 versus -3.61 mL/min/1.73 m²); the group difference was 1.27 mL/min/1.73 m² (95% CI 0.86-1.68).
 - The analysis of the REPRISE trial, and a post-hoc analysis of the TEMPO trial, showed that tolvaptan (Jynarque) may extend the time until stage 5 CKD (ie, eGFR <15 mL/min/1.73 m²) from six to nine years among patients who start tolvaptan with an eGFR <60 mL/min/1.73 m², and, even longer among those who start tolvaptan earlier.
 - Clinical trial criteria for rapidly progressive ADPKD
 - i. Age 18-50 AND eGFR ≥ 60 mL/min/1.73m² AND Total Kidney Volume ≥ 750 mL
 - ii. Age 18-55 AND eGFR 25 to 65 mL/min/1.73m²
 - iii. Age 56-65 AND eGFR 25 to 44 mL/min/1.73m² AND documented eGFR decline of more than 2.0 mL/min/1.73m² per year

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- The pivotal trials for Jynarque did not involve patients with Stage 5 CKD (glomerular filtration rate [GFR] < 15 mL/min/1.73 m² or receiving dialysis).
- IV. Tolvaptan (Jynarque) is a part of a Risk Evaluation and Mitigation Strategy (REMS) program to monitor for liver injury.
 - V. Tolvaptan (Jynarque) should not be used off-label for other diagnoses due to lack of evidence, and risk of adverse events.
 - VI. In clinical trials, outcomes included the reduction in rate of total kidney volume growth, the slowed rate of kidney function decline, improvement in renal function, a change in mean arterial blood pressure, and change in renal pain. Stability of disease, or improvement in at least one of these measures, is indicative of treatment response. Additionally, fatal liver injury is a significant safety concern of Jynarque; liver function tests should be monitored periodically.

Investigational or Not Medically Necessary Uses

I. Hyponatremia

- A. Samsca, is a tolvaptan formulation that is FDA approval for the treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium of less than 125 mEq/L or less marks hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure and syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Jynarque has not been evaluated for treatment of hyponatremia.

References

1. Jynarque [Prescribing Information]. Tokyo, Japan: Otsuka Pharmaceutical Co. April 2018
2. Muto S, Kawano H, Higashihara E., et al. The effect of tolvaptan on autosomal dominant polycystic kidney disease patients: a subgroup analysis of the Japanese patient subset from TEMPO 3:4 trial. Clin Exp Nephrol. 2015;19(5):867-877.
3. Torres, VE, Chapman, AB, Devuyst, O, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. The New England journal of medicine. 2012 Dec 20;367(25):2407-18. PMID: 23121377
4. Torres VE., Chapman AB., Devuyst O., et al. Tolvaptan in later-stage autosomal dominant polycystic kidney disease. N Engl J Med. 2017;377:1930-1942.
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Policy Implementation/Update:

Action and Summary of Changes	Date
Added generic tolvaptan to policy. Added requirement for generic tolvaptan to step through brand tolvaptan (Jynarque). Realigned QL table format.	07/2025
Removed the requirement for imaging or genetic test to confirm diagnosis. Updated language to align with FDA labeling. Updated initial approval from 6 months to 12 months.	03/2025
Updated to policy format. Added the following: quantity limits for new 15 mg and 30 mg tablet, therapy to be prescribed by or in consultation with nephrologist, limited use to reflect patient population included in clinical trial (i.e. rapidly progressing ADPKD and do not have stage 5 CKD).	05/2019
Date created	05/2018

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP099

Description

Tolvaptan (Samsca) is an orally administered vasopressin V2-receptor antagonist which causes an increase in urine water excretion that results in an increase in free water clearance (aquaresis), a decrease in urine osmolality, and a resulting increase in serum sodium concentrations.

Length of Authorization

- Initial: one month
- Renewal: no renewal

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
tolvaptan (Samsca)	15 mg tablet	Hypervolemic or euvoletic hyponatremia	30 tablets/30 days*
	30 mg tablet		60 tablets/30 days*

*Therapy should not be continued past 30 days.

Initial Evaluation

- I. Tolvaptan (Samsca) may be considered medically necessary when the following criteria below are met:
 - A. Member is 18 years of age or older; **AND**
 - B. Medication is prescribed by, or in consultation with, an endocrinologist or nephrologist; **AND**
 - C. Medication was initiated in the hospital; **AND**
 - D. The requested treatment course will not exceed a 30-day duration per FDA recommendation; **AND**
 - E. A diagnosis of **clinically significant hypervolemic or euvoletic hyponatremia** when the following are met:
 1. Serum sodium is less than 125 mEq/L; **OR**
 2. Serum sodium is greater than 125 mEq/L **and** patient has symptomatic hyponatremia (e.g., nausea, vomiting, headache, lethargy, confusion) that has resisted correction with fluid restriction
- II. Tolvaptan (Samsca) is considered investigational when used for all other conditions, including but not limited to:
 - A. Autosomal Dominant Polycystic Kidney Disease (ADPKD)
 - B. Patients requiring intervention to raise serum sodium urgently to prevent or to treat serious neurological symptoms

Supporting Evidence

- I. Per the label, tolvaptan (Samsca) is indicated for the treatment of clinically significant hypervolemic and euvoletic hyponatremia (serum sodium <125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure and Syndrome of Inappropriate Antidiuretic Hormone (SIADH).
- II. Safety and effectiveness of tolvaptan (Samsca) in pediatric patients has not been established.
- III. Per the label, patients should be in a hospital for initiation and re-initiation of therapy to evaluate the therapeutic response and because too rapid correction of hyponatremia can cause osmotic demyelination resulting in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma and death.
- IV. To minimize the risk of liver injury, tolvaptan (Samsca) should not be administered for more than 30 days. Based largely on the hepatic injury noted in the TEMPO trial, on April 2013 the FDA recommended that: "treatment should be stopped if the patient develops signs of liver disease. Treatment duration should be limited to 30 days or less, and use should be avoided in patients with underlying liver disease, including cirrhosis".
- V. It has not been established that raising serum sodium with tolvaptan (Samsca) provides a symptomatic benefit to patients.

Investigational or Not Medically Necessary Uses

- I. Autosomal Dominant Polycystic Kidney Disease (ADPKD)
 - A. Jynarque (tolvaptan) is another tolvaptan product that is indicated to slow kidney function decline in adults at risk of rapidly-progressing ADPKD; however, the recommended dosing in Jynarque differs from the Samsca product. Per the tolvaptan (Samsca) label, because of the risk of hepatotoxicity, tolvaptan should not be used for ADPKD outside of the FDA-approved REMS.
- II. Patients requiring intervention to raise serum sodium urgently to prevent or to treat serious neurological symptoms.
 - A. Tolvaptan (Samsca) has not been studied in a setting of urgent need to raise serum sodium acutely.

References

1. Samsca [prescribing information]. Rockville, MD: Otsuka Pharmaceuticals; April 2018.
2. Torres VE, Chapman AB, Devuyst O, et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. *N Engl J Med*. 2012;367(25):2407-18.
3. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. Verbalis JG, Goldsmith SR, Greenberg A, Korzelius C, Schrier RW, Sterns RH, Thompson CJ. <https://pubmed.ncbi.nlm.nih.gov/24074529/> *Am J Med*. 2013;126:0.3. Spasovski G, Vanholder R, Allolio B, et al. Clinical practice guideline on diagnosis and treatment of hyponatraemia. *Nephrol Dial Transplant* 2014; 29 Suppl 2:i1.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	11/2019

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP308

Split Fill Management*

Description

Tovorafenib (Ojemda) is a type II RAF kinase inhibitor of mutant BRAF V600E, wild-type BRAF, and wild-type CRAF kinases.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
tovorafenib (Ojemda)	Relapsed or refractory pediatric low-grade glioma (LGG) harboring a BRAF fusion or rearrangement, or BRAF V600 mutation	25 mg/mL suspension	See Appendix*
		100 mg tablet	24 tablets/28 days

*Please note that the dose is based on body surface area (BSA). Please see appendix for dosing limits.

Initial Evaluation

- I. **Tovorafenib (Ojemda)** may be considered medically necessary when the following criteria are met:
 - A. Member is 6 months of age or older; **AND**
 - B. Medication is prescribed by, or in consultation with, an oncologist; **AND**
 - C. Medication will not be used in combination with any other oncology therapy; **AND**
 - D. Documentation of member's weight and height; **OR**
 1. Documentation of the member's body surface area (BSA); **AND**
 - E. If request is for suspension, provider attests member is unable to swallow tablets; **AND**
 - F. A diagnosis of **relapsed or refractory pediatric low-grade glioma (pLGG)** when the following are met:
 1. Documentation of BRAF fusion or rearrangement, or BRAF v600 mutation; **AND**
 2. Member has progressive disease after trial of a prior systemic therapy [e.g., carboplatin/vincristine, vinblastine, carboplatin/vincristine/etoposide, dabrafenib (Tafinlar)/trametinib (Mekinist), etc.]; **AND**
 3. Treatment with a second-line of chemotherapy (e.g., carboplatin/vincristine, vinblastine, carboplatin/vincristine/etoposide) has been ineffective, contraindicated, or not tolerated; **AND**
 4. Provider attestation that member is not eligible for any ongoing clinical trials for the treatment of BRAF-mutated relapsed or refractory low-grade glioma (pLGG)

- II. Tovorafenib (Ojemda) is considered investigational when used for all other conditions, including but not limited to:
 - A. Tovorafenib (Ojemda) used in combination with another oncology therapy
 - B. Pediatric low-grade glioma (LGG) 1st line systemic therapy
 - C. High grade glioma (HGG)
 - D. Melanoma
 - E. Langerhans cell histiocytosis
 - F. Craniopharyngioma

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Member has exhibited response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread; **AND**
- IV. Documentation of member's weight and height; **OR**
 - 1. Documentation of the member's body surface area (BSA); **AND**
- III. If request is for suspension, provider attests member is unable to swallow tablets; **AND**
- V. Medication will not be used in combination with any other oncology therapy

Supporting Evidence

- I. Tovorafenib (Ojemda) is being evaluated in several clinical trials; however, efficacy, pharmacokinetic, and pharmacodynamic parameters have been studied in pediatric patients six months of age and older. Safety and efficacy in adults has not been established at this time.
- II. Given the specialized, high-touch care, nuances of treatment, monitoring, and consideration for patient specific goals required for the treatment of BRAF mutated cancers, therapy choices should be directed by an oncologist.
- III. Tovorafenib (Ojemda) has not been adequately studied in combination with any other oncology therapy, therefore, use of tovorafenib (Ojemda) in combination with other oncology treatments is considered experimental and investigational at this time.
- IV. The dosing regimen of tovorafenib (Ojemda) is dependent on the patient's body surface area (BSA) for once weekly administration. Documentation of the member's BSA is required to establish the correct dosing parameters.
- V. Tovorafenib (Ojemda) is a type II RAF kinase inhibitor FDA-approved for the treatment of patients six months of age and older with relapsed or refractory pediatric low-grade glioma (LGG) harboring a BRAF fusion or rearrangement, or BRAF v600 mutation. It is administered as a once weekly suspension or tablet.
- VI. Pediatric low-grade gliomas (pLGG) are the most frequent solid malignant tumors diagnosed in children and young adults with an estimated 2,600 patients diagnosed in 2020. Although overall survival averages from 80-90%, prognosis is influenced by many factors including the degree of tumor resection achieved, histological and molecular tumor classification, or presence of disseminated disease. Children will typically present with seizures or focal neurological deficits:

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weakness, difficulty swallowing, sensory loss, visual impairment, or changes in academic/athletic performance.

- VII. Surgery is the first treatment modality for almost 80% of all LGG patients. Following surgery, observation may be the only treatment indicated. When there is residual disease, or for those where surgery isn't an option, drug therapy is indicated. Chemotherapy combinations of vincristine and carboplatin are standard per United Kingdom (UK) guidelines and are typical practice in the United States (U.S.). There are currently no standardized guidelines for pLGG in the U.S. Results of chemotherapy trials are consistent, showing overall survival rates between 70-95%, but a low progression free survival at around 45% at 5 years. Other approved therapies for first line systemic treatment include dabrafenib (Tafinlar)/trametinib (Mekinist) in patients aged ≥ 1 year with LGG with a BRAF V600E mutation. For those with residual tumor present, 35% to 55% will relapse or be refractory and may require second line treatment. Tovorafenib (Ojemda) was studied in a Phase 2 open-label trial in 77 pediatric patients with an activating BRAF alteration who had previously been treated with at least one line of prior systemic therapy with evidence of radiographic progression. The primary efficacy outcome was the objective response rate (ORR) as assessed by Response Assessment in Neuro-Oncology for high-grade gliomas (RANO-HGG) criteria, though overall response rate (ORR) assessed by Response Assessment in Pediatric Neuro-Oncology for low-grade gliomas (RAPNO-LGG) is included in the FDA label. Baseline characteristics of the trial participants: median age was nine years (range, 1–24), white (58%), astrocytic tumors (93%), KIAA1549:BRAF fusion (74%), BRAF V600E mutation (16%), median of three lines of prior therapy (range, 1–10), with 61% having received a prior MEK and/or BRAF inhibitor. The ORR as assessed by RAPNO-LGG criteria was 51% with partial response (37%) and minimal response (14%) driving the efficacy. Thirty percent of participants were able to establish stable disease. The median duration of response was 13.8 months (11.3, NR) with a median time to response of 5.3 months (1.6, 11.2).
- VIII. The most common adverse reactions (AEs) were rash (77%), hair color changes (76%), fatigue (55%), viral infection (55%), and vomiting (50%). Serious adverse reactions occurred in 45% of patients who received tovorafenib (Ojemda). Serious adverse reactions in $>2\%$ of patients included viral infection (9%), pneumonia (4%), and sepsis (4%). Tovorafenib (Ojemda) showed a 57% dose interruption rate in clinical trials and a 24% dose reduction rate due to intolerable AEs. Permanent discontinuation only occurred in 7% of patients. Tumor hemorrhage (one patient; which was a fatal AE) and reduction in growth velocity (two patients).
- IX. As pLGG tumors undergo senescence in adults, the goal of therapy is to stabilize the tumor in pediatric and adolescent patients while retaining quality of life and physical functioning. A partial response, minor response, and/or stable disease may be considered clinically meaningful if there is some degree of tumor shrinkage/stabilization paired with a lack of progression of symptoms (e.g., neurological deficits, vision changes). The single-arm, open-label trial design makes the data observational; however, this concern may be mitigated as pLGG tumors are not expected to regress without treatment. The impact of tovorafenib (Ojemda) on long term efficacy, morbidity, and mortality remains unknown. Coupled with potential bias due to a small sample size, the overall confidence in a substantial benefit is considered low but the data may be sufficient to make healthcare decisions.
- X. Current second-line systemic treatment options include additional chemotherapy, retreatment with prior chemotherapy agents if there is good response and a prolonged period between

treatment and subsequent relapse or progression, or combination BRAF/MEK inhibitors (e.g., dabrafenib (Tafinlar)/trametinib (Mekinist)).

- XI. Second-line chemotherapy regimens have been evaluated in multiple clinical trials with known side effect profiles. While treatment with second-line chemotherapy may be more cost effective than newer targeted therapies and is required prior to allowing coverage to tovorafenib (Ojemda) in eligible patients, individual patient specific factors should be taken into account when considering further treatment with chemotherapy in the relapsed/refractory setting. Examples of patient specific factors that may make additional lines of chemotherapy inappropriate include previous therapy intolerance, a caregiver's inability to take member to appointments, logistical considerations, etc.

Investigational or Not Medically Necessary Uses

- I. Tovorafenib (Ojemda) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
- A. Tovorafenib (Ojemda) used in combination with another oncology therapy
 - B. Pediatric low-grade glioma (LGG) 1st line systemic therapy
 - i. Tovorafenib (Ojemda) is currently under investigation for the treatment of pLGG harboring an activating RAF alteration who require first-line systemic therapy. LOGGIC/FIREFLY-2 is a two-arm, randomized, open-label, multicenter, global, Phase 3 trial to evaluate the efficacy, safety, and tolerability of tovorafenib (Ojemda) monotherapy vs. current standard of care (SoC) chemotherapy in patients < 25 years of age. Primary completion is expected in June 2026. Requests for this indication are considered experimental and investigational at this time.
 - C. High grade glioma (HGG)
 - i. There is currently no active trial evaluating the use of tovorafenib (Ojemda) in patients with high grade glioma (HGG). There is insufficient evidence to support to the safety and efficacy of tovorafenib (Ojemda) in this disease space.
 - D. Melanoma
 - i. Tovorafenib (Ojemda) is currently under investigation in a Phase 1b/2, multi-center, open label umbrella study of patients ≥12 years of age with recurrent, progressive, or refractory melanoma or other solid tumors with alterations in the key proteins of the RAS/RAF/MEK/ERK pathway, referred to as the MAPK pathway. Primary completion is expected in December 2025. Requests for this indication are considered experimental and investigational at this time.
 - E. Langerhans cell histiocytosis
 - i. Tovorafenib (Ojemda) is currently under investigation in a Phase 2 trial of patients with R/R Langerhans cell histiocytosis. Primary completion is expected in May 2025. Requests for this indication are considered experimental and investigational at this time.
 - F. Craniopharyngioma
 - i. Tovorafenib (Ojemda) is currently under investigation in combination with PD-1 (nivolumab) for the treatment of young adults with craniopharyngioma (NCT05465174). Results are not expected until March 2027. Requests for this indication are considered experimental and investigational at this time.

Appendix

Table 1: Recommended Dosage for tovorafenib (Ojemda) Oral Tablets Based on Body Surface Area

Body Surface Area (m ²)	Recommended Dosage
0.30-0.89	Administer tovorafenib (Ojemda) oral suspension once weekly
0.90-1.12	400 mg once weekly
1.13-1.39	500 mg once weekly
≥ 1.40	600 mg once weekly

Table 2: Recommended Dosage for tovorafenib (Ojemda) Oral Suspension Based on Body Surface Area

Body Surface Area (m ²)	Dose Volume (mL)	Recommended Dosage	Quantity Level Limit
0.30-0.35	5	125 mg once weekly	48 mL/28 days
0.36-0.42	6	150mg once weekly	48 mL/28 days
0.43-0.48	7	175 mg once weekly	48 mL/28 days
0.49-0.54	8	200 mg once weekly	48 mL/28 days
0.55-0.63	9	225 mg once weekly	48 mL/28 days
0.64-0.77	11	275 mg once weekly	48 mL/28 days
0.78-0.83	12	300 mg once weekly	48 mL/28 days
0.84-0.89	14	350 mg once weekly	96 mL/28 days
0.90-1.05	15	375 mg once weekly	96 mL/28 days
1.06-1.25	18	450 mg once weekly	96 mL/28 days
1.26-1.39	21	525 mg once weekly	96 mL/28 days
≥ 1.40	24	600 mg once weekly	96 mL/28 days

References

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6. van Tilburg CM, Kilburn LB, Perreault S, et al. LOGGIC/FIREFLY-2: a phase 3, randomized trial of tovorafenib vs. chemotherapy in pediatric and young adult patients with newly diagnosed low-grade glioma harboring an activating RAF alteration. BMC Cancer. 2024;24(1):147. Published 2024 Jan 30.

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
encorafenib (Braftovi®), binimetinib (Mektovi®)	Malignant melanoma, unresectable or metastatic, with BRAF V600E or V600K mutation, combination therapy; Metastatic colorectal cancer, with BRAF V600E mutation, combination therapy (Braftovi only)
Dabrafenib (Tafinlar), Trametinib (Mekinist)	Anaplastic thyroid carcinoma, advanced or metastatic, BRAF V600E mutated, combination therapy; Melanoma, adjuvant therapy for

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	malignant disease, BRAF V600E or K mutated, combination therapy; Melanoma, malignant unresectable or metastatic disease, BRAF V600E or K mutated, combination therapy; Melanoma, malignant unresectable or metastatic disease, BRAF V600E or K mutated, monotherapy in BRAF treatment naïve patients; Non-small cell lung cancer, metastatic, BRAF V600E mutated, combination therapy; Unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options; Pediatric low-grade glioma (LGG) with a BRAF V600E mutation, combination therapy
cobimetinib (Cotellic®), vemurafenib (Zelboraf®)	Unresectable or metastatic melanoma with a BRAF V600E or V600K mutation; Histiocytic neoplasms in adults (Cotellic only); Erdheim-Chester disease with a BRAF v600 mutation (Zelboraf only)
Selumetinib (Koselugo)	Neurofibromatosis type 1 (NF1)

Policy Implementation/Update:

Action and Summary of Changes	Date
Added split fill edits. Added criteria to require provider attestation member is unable to swallow tablets if requesting suspension formulation.	02/2025
Policy created	08/2024

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP247

Description

Tralokinumab (Adbry) is a subcutaneous fully human monoclonal antibody of interleukin-13 (IL-13).

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
tralokinumab (Adbry)	150 mg/mL prefilled syringe	Moderate-to-Severe Atopic Dermatitis	Adult
			First Month: 6 mL (6 syringes)/28 days Maintenance: 4 mL (4 syringes)/28 days*
	300 mg/2mL single dose autoinjector pen		First Month: 6 mL (3 autoinjectors)/28 days Maintenance: 4 mL (2 autoinjectors)/28 days*
	150 mg/mL prefilled syringe		Pediatric (12 to 17 years old)
			First Month: 4 mL (4 syringes)/28 days Maintenance: 2 mL (2 syringes)/28 days
	300 mg/2mL single dose autoinjector pen		First Month: 4 mL (2 autoinjectors)/28 days Maintenance: 2 mL (1 autoinjector)/28 days

*300 mg (2 syringes)/28 days may be considered for patients under 100 kg who achieve clear skin

Initial Evaluation

- I. **Tralokinumab (Adbry)** may be considered medically necessary when the following criteria are met:
 - A. Member is 12 years of age or older; **AND**
 - B. Medication is prescribed by, or in consultation with, a dermatologist or allergist; **AND**
 - C. The medication prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat atopic dermatitis or another auto-immune condition (e.g. Otezla, Xeljanz, Olumiant); **AND**
 - D. A diagnosis of **moderate-to-severe atopic dermatitis** when the following are met:
 1. Body surface area (BSA) involvement of at least 10%; **OR**
 - i. Involves areas of the face, ears, hands, feet, or genitalia; **AND**
 2. Treatment with at least **TWO** of the following groups has been ineffective or not tolerated, or **ALL** are contraindicated:
 - i. Group 1: topical corticosteroids of at least medium/moderate potency (e.g., clobetasol, betamethasone, halobetasol)

- ii. Group 2: topical calcineurin inhibitors (e.g., tacrolimus ointment, pimecrolimus cream)
 - iii. Group 3: topical PDE-4 inhibitor (crisaborole [Eucrisa]); **AND**
 - 3. Treatment with dupilumab (Dupixent) and upadacitinib (Rinvoq) have been ineffective, contraindicated, or not tolerated.
- II. Tralokinumab (Adbry) is considered investigational when used for all other conditions, including but not limited to:
- A. Asthma or COPD
 - B. Nasal polyps
 - C. Pediatric or adolescent atopic dermatitis
 - D. Ulcerative colitis
 - E. Alopecia areata

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. The medication prescribed will not be used in combination with other biologics or other non-biologic specialty medication used to treat atopic dermatitis or another auto-immune condition (e.g. Otezla, Xeljanz, Olumiant); **AND**
- IV. Member has exhibited improvement or stability of disease symptoms (e.g., improvement in IGA score from baseline, BSA involvement, pruritis symptoms)

Supporting Evidence

- I. Atopic dermatitis (AD), also known as atopic eczema, is an inflammatory skin condition most frequently occurring in pediatric patients. It manifests with pruritis, dry skin, crusting, and serous oozing causing chronic scratching which leads to blister formation, skin thickening (lichenification), fissuring, or lesions. This condition is associated with elevated serum IgE and it is often a comorbid condition with asthma and allergic conditions.
- II. Treatments for mild-to-moderate AD include topical corticosteroids (TCS), topical calcineurin inhibitors (TCI), phototherapy, and/or crisaborole (Eucrisa) – a PDE4 inhibitor. Symptomatic treatments include oral and topical antihistamines and sleep aids for nighttime pruritus. Treatment choice between these products is dependent on severity, location, and other patient specific factors (e.g., allergies, age). According to AAD guidelines, TCIs may be preferable to TCS in patients with recalcitrance to steroids, sensitive areas involved, steroid-induced atrophy, and long-term uninterrupted topical steroid use.
- III. Treatment for moderate-to-severe disease not amenable to topicals includes systemic immunosuppressants (e.g., corticosteroids, cyclosporine, methotrexate, azathioprine, mycophenolate mofetil) and dupilumab (Dupixent), a biologic IgG4 that is FDA-approved for

- pediatrics and adults as a biologic option for moderate-to-severe AD. Currently, there are no head to head trials evaluating safety and/or efficacy differences or superiority between tralokinumab (Adbry) and other therapies. Dupilumab (Dupixent) has an established safety and efficacy profile for the treatment of atopic dermatitis and is approved down to six years of age.
- IV. There may be patient specific scenarios in which the use of additional topical agents following failure of one class of topical agents would be impractical. Insight from dermatology specialists indicate that patients who have at least 15% BSA involvement, or involvement in sensitive areas (e.g., eyelids, axilla, genitals, gluteal cleft), and have severe disease are potential candidates for systemic biologic therapy. Severe disease, as defined by NICE guidelines, includes widespread areas of dry skin, incessant itching, redness (with or without excoriation, extensive skin thickening, bleeding, oozing, cracking, and alteration of pigmentation), and severe limitation of everyday activities and psychosocial functioning, nightly loss of sleep; severe disease can also be classified as physician's global assessment (PGA) score of 4.0. Additionally, administration of topical agents may become impractical for patients with high disease burden (BSA $\geq$ 20%), considering twice daily administration is necessary for non-steroid topical agents for optimal efficacy.
 - V. Tralokinumab (Adbry) was evaluated in three randomized, double-blind, placebo-controlled, Phase III trials. Two as monotherapy (ECZTRA 1 and ECZTRA 2) and one in addition to topical corticosteroids (ECZTRA 3). Medication was administered as a 600 mg loading dose on day 0, followed by 300 mg every two weeks or placebo. In ECZTRA 1 and 2: at 16 weeks, responders continued on and were re-randomized to continue 300 mg every two weeks, change to 300 mg every four weeks, or placebo. In ECZTRA 3: at 16 weeks responders were re-randomized to tralokinumab (Adbry) every two or four weeks. All patients included in the trials were adults, and safety and efficacy in adolescent and pediatric patients is unknown. Patients included in the trials had moderate-to-severe AD (IGA 3-4) with BSA of at least 10% and had insufficient response to topical therapies. The majority had utilized several topical therapies, systemic immunosuppressants and phototherapy. Patients in ECZTRA 3 (6%) had history of use of dupilumab (Dupixent), and patients in ECZTRA 1 and 2 did not have a history of use.
 - VI. Tralokinumab (Adbry) showed positive outcomes in all three trials with regard to morbidity, symptom control, and quality of life parameters via proportion of patients with an IGA of 0 or 1, proportion of patients meeting EASI 75, SCORAD change, change in NRS score from baseline, DLQI, and in ECZTRA 3 – TCS utilization - further details on measurement tools are provided in the appendix below.
 - VII. ECZTRA 1 and 2: When responders of therapy were re-randomized to tralokinumab (Adbry) every two weeks, every four weeks, or placebo, the majority of patients on every two-week therapy maintained response, while there was a nonsignificant difference in response maintained between the every-two-week and placebo arms for maintenance in ECZTRA 1. This was attributed to patients being counted as non responders if any other therapy (e.g., TCS) was utilized. Additionally, many of those that were transitioned to placebo maintained response out to week 52. There was a difference seen in maintenance of response in ECZTRA 2 vs. placebo.
 - VIII. ECZTRA 3: Those that did not achieve the endpoints at week 16 were allowed to continue therapy, of those patients, 30.5% met IGA 0/1 and 55.8% met EASI 75 at week 32. Additionally, after re-randomization to tralokinumab (Adbry) every two weeks or every four weeks, 90% and

78% of patients maintained IGA 0/1, respectively, and 92.2% and 90.8% of patients maintained EASI 75, respectively.

- IX. The overall incidence of adverse events (AE) was similar to placebo in clinical trials. Common AE (>5%): AD, URTI, skin infection, pruritus, headache, and conjunctivitis. Eye disorders are notable AE for tralokinumab (Adbry) as there was more URI (up to 3% greater) and conjunctivitis (up to 5% greater) seen in tralokinumab (Adbry) than in placebo. In addition, there were also eight cases of keratoconjunctivitis and keratitis compared to the one case seen on placebo. These AE's are seen similarly for dupilumab (Dupixent). Skin infections overall, as well as those that required systemic treatment, were greater in the placebo group. A long-term extension trial evaluating safety (EzTEND) is expected to be complete in September 2021.
- X. There is lack of head-to-head clinical trial data for the AD FDA-approved therapies, and superior safety and efficacy of any product cannot be confidently concluded. Thus, it is reasonable that, pending no contraindication to therapy, preferred therapies be based on cost-effectiveness.

Investigational or Not Medically Necessary Uses

- I. Tralokinumab (Adbry) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Asthma or COPD
 - B. Nasal polyps
 - C. Pediatric or adolescent atopic dermatitis
 - D. Ulcerative colitis
 - E. Alopecia areata

Appendix

Outcomes Key		
Name	Explanation	Use and Significance
IGA: Investigators Global Assessment Scale	Five-point scale assesses AD severity: 0-4, 0 is clear and 4 is severe. Decrease in score indicates improvement of AD signs and symptoms.	-Used for clinical trials -Clinically important difference is a 1-point change
EASI: Eczema Area and Severity Index	Scale assesses severity and extent of AD, 0-72 points. EASI 75 = 75% improvement from baseline. Measures 4 characteristics: erythema, infiltration/papulation, excoriations, lichenification, each on a scale of 0-3. These have different weight for each of the four body regions and are summed.	-Used for clinical trials -Clinically important difference is a 7-point change
SCORAD: Scoring Atopic Dermatitis	Tool used to evaluate severity and extent of AD. Assesses 3 components: BSA, severity, and symptoms. Extent is assessed as a percentage of each defined body area and reported as a sum. Maximum score is 100% for extent. The severity of six symptoms is assessed using a four-point scale: erythema, swelling, oozing/crusting, excoriation, skin thickening/lichenification, dryness. Severity has a maximum score of 18 points. Symptoms are recorded on a scale of 0-10, where 10 is the worst score imaginable. Entire score has a maximum of 103, higher scores=more severe condition.	-Used in clinical trials -Clinically important difference is a ~9 point change.
NRS: Pruritus Numerical Rating Scale	Tool used by patients to report the intensity of their itch. A scale of 0-10: 10 being worst itch imaginable. Often measured as a weekly average of the peak daily pruritus, tracked throughout a trial.	-Used in clinical trials -Clinically importance difference is 3-4 points.
DLQI: Dermatology Life Quality Index	Tool used widely in dermatology. 10 item questionnaire, assesses 6 aspects: feelings, activities, leisure, work/ school performance, personal relationships, treatment. Max	-Sometimes used in practice.

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	score per question is 3. DLQI is calculated by summing of scores for a maximum of 30. 0-1: no effect, 21-30: extremely large effect.	-Clinically important difference is 2-7-point change.

References

1. Wollenberg A., Blauvelt A., Guttman-Yassky E., et al. Tralokinumab for moderate-to-severe atopic dermatitis: results from two 52-week, randomized, double-blind, multicenter, placebo-controlled phase III trials (ECZTRA 1 and ECZTRA 2). Br J Dermatol. 2020 Sep 30. doi: 10.1111/bjd.19574. Epub ahead of print. PMID: 33000465.
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4. Eichenfield L., Tom, W., Chamlin S., et al. Guidelines of care for the management of atopic dermatitis. JAAD. 2014 Feb 1. 70(2): 338-351.
5. Clinical Review Report: Dupilumab (Dupixent): (Sanofi-Aventis Canada Inc.): Indication: Moderate-to-severe atopic dermatitis (AD) [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2018 Jul. Appendix 5, Validity of Outcomes Measures. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK539234/>
6. Dupixent [Prescribing Information]. Regeneron Sanofi Genzyme. Tarrytown, NF. January 2021.

Policy Implementation/Update:

Action and Summary of Changes	Date
Added 300mg/2mL autoinjector pen to policy	07/2024
Updated criteria to include age expansion to 12 years and older based on FDA approval; updated supportive evidence.	03/2024
Live 04/01/2024: Updated policy to remove upadacitinib (Rinvoq) as a preferred therapy	02/2024
Review conducted. Update to supporting evidence	02/2023
Added requirement that Adbry will not be used in combination with other biologic or non-biologic specialty medications to initial criteria	10/2022
Policy update to include upadacitinib (Rinvoq) as a preferred therapy	01/2022
Policy update to prefer Dupixent	05/2021
Policy created	02/2021

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP100

Description

Trametinib (Mekinist) is an orally administered mitogen-activated extracellular signal which regulates kinase 1 (MEK1) and MEK2 activation and MEK1 and MEK2 activity, while also inhibiting BRAF V600 mutation-positive melanoma cell growth. Dabrafenib (Tafinlar) is an orally administered BRAF V600 inhibitor. When used in combination, there is greater and prolonged inhibition compared to either drug alone.

Length of Authorization

- Initial: Six months
- Renewal:
 - i. Six months for adjuvant treatment of melanoma that had lymph node involvement and was completely resected. One time renewal only (i.e., one total year of therapy authorized).
 - ii. 12 months for all other indications

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
trametinib (Mekinist)	Anaplastic thyroid carcinoma, advanced or metastatic, BRAF V600E mutated, combination therapy	0.5 mg tablet	90 tablets/30 days
	Melanoma, adjuvant therapy for malignant disease, BRAF V600E or K mutated, combination therapy	2 mg tablet	30 tablets/30 days
	Melanoma, malignant unresectable or metastatic disease, BRAF V600E or K mutated, combination therapy	0.05 mg/mL solution	1,200 mL/30 days
dabrafenib (Tafinlar)	Melanoma, malignant unresectable or metastatic disease, BRAF V600E or K mutated, monotherapy in BRAF treatment naïve patients	50 mg capsule	120 capsules/30 days
	Non-small cell lung cancer, metastatic, BRAF V600E mutated, combination therapy	75 mg capsule	
	Unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options	10 mg soluble tablet	360 tablets/30 days
	Pediatric low-grade glioma (LGG) with a BRAF V600E mutation, combination therapy		

Initial Evaluation

- I. **Trametinib (Mekinist) and dabrafenib (Tafinlar)** may be considered medically necessary in combination when the following criteria below are met:
 - A. The medication is prescribed by, or in consultation with, an oncologist; **AND**
 - B. The prescriber attests trametinib (Mekinist) and dabrafenib (Tafinlar) will be used in combination AND no other oncolytic medication will be used concurrently; **AND**
 - C. The member has not previously progressed on any prior BRAF-inhibitor therapy (e.g., vemurafenib); **AND**
 - D. A diagnosis of one of the following:
 1. **Anaplastic thyroid carcinoma; AND**
 - i. The member is 18 years of age or older; **AND**
 - ii. The disease has been tested and shown to have BRAF V600E mutation; **AND**
 - a. The disease is metastatic (stage IV); **OR**
 - b. The disease is locally advanced (stage IVA or IVB); **AND**
 - i. The member has received standard of care for the condition (e.g., surgery, radiation therapy, chemotherapy); **OR**
 - ii. There are no satisfactory locoregional treatment options; **OR**
 2. **Melanoma; AND**
 - i. The member is 18 years of age or older; **AND**
 - ii. The disease has been tested and shown to have BRAF V600E or V600K mutation; **AND**
 - iii. Melanoma is advanced (stage III), metastatic (stage IV), or unresectable; **OR**
 - a. Melanoma has lymph node involvement and will be used as adjuvant treatment after complete resection; **OR**
 3. **Non-small cell lung cancer; AND**
 - i. The member is 18 years of age or older; **AND**
 - ii. The disease has been tested and shown to have V600E mutation.
 4. **Pediatric low-grade glioma (LGG); AND**
 - i. The member is between the ages of 1 and 17 years; **AND**
 - ii. The disease has been tested and shown to have V600E mutation; **AND**
 - iii. Disease has progressed following surgical excision; **OR**
 - a. Attestation the member is not a candidate for surgical intervention; **AND**
 - iv. Attestation the member has not undergone prior systemic or radiotherapy- II. Trametinib (Mekinist) and dabrafenib (Tafinlar) are considered not medically necessary when criteria above are not met and/or when used for:
 - A. Treatment after prior BRAF inhibitor therapy

- III. Trametinib (Mekinist) and dabrafenib (Tafinlar) are considered investigational when used for all other conditions, including but not limited to:
- A. Erdheim Chester Disease
 - B. Leukemias, lymphomas
 - C. Neurofibromatosis type 1 (NF1)
 - D. BRAF V600E mutated unresectable or metastatic solid tumors
 - E. Pediatric Low-Grade Glioma, second line systemic therapy

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. The prescriber attests trametinib (Mekinist) and dabrafenib (Tafinlar) will be used in combination AND no other oncolytic medication will be used concurrently; **AND**
- IV. Documentation is provided indicating disease response to therapy, as defined by stabilization of disease or decrease in size of tumor or tumor spread.

Supporting Evidence

- I. Dabrafenib (Tafinlar) plus trametinib (Mekinist) has been evaluated in several clinical trials in adults. Pharmacokinetic and pharmacodynamic parameters have been studied in pediatric patients 6 years of age and older for the treatment of BRAF V600E mutated unresectable or metastatic solid tumors. However, safety and efficacy in pediatrics has not been established.
- II. Given the specialized, high-touch care, nuances of treatment, monitoring, and consideration for patient specific goals required for the treatment of BRAF mutated cancers, therapy choices should be directed by a specialist.
- III. Per the respective FDA labels dabrafenib (Tafinlar) and trametinib (Mekinist) are indicated as single agents for the treatment of unresectable or metastatic melanoma with BRAF V600E mutations as detected by an FDA-approved test. However, efficacy data to support non-combination use of these products is low quality. Trametinib (Mekinist) did not show to have efficacy in a trial evaluating as second-line therapy after previous therapy with BRAF inhibitors.
- IV. Use of BRAF inhibitors (e.g., vemurafenib [Zelboraf], encorafenib [Braftovi]) therapy after disease progression on dabrafenib (Tafinlar) and trametinib (Mekinist), or vice versa, has not yet been evaluated for safety and efficacy in quality clinical trials.

Treatment of Anaplastic Thyroid Carcinoma

- V. A study of dabrafenib (Tafinlar) administered with trametinib (Mekinist) evaluated subjects with thyroid cancer that were BRAF V600E mutation positive. The open-label, single-arm trial included those that were locally advanced, unresectable, or metastatic with no locoregional treatment options. Primary outcomes were ORR and DOR.

Treatment of Melanoma

- VI. The METRIC study evaluated trametinib (Mekinist) as monotherapy in V600E or V600K mutation-positive, unresectable, or metastatic melanoma. It was an open-label trial against chemotherapy (dacarbazine or paclitaxel). The primary outcome was progression-free survival (PFS), and statistically favored trametinib (Mekinist).
- VII. The COMBI-d study was a double-blind, active controlled trial of dabrafenib (Tafinlar) plus trametinib (Mekinist) versus dabrafenib (Mekinist) alone. Subjects included had unresectable or metastatic BRAF V600E or V600K mutation-positive cutaneous melanoma. Combination therapy was statistically favorable in PFS and overall-survival (OS).
- VIII. The COMBI-AD trial evaluated dabrafenib (Tafinlar) with trametinib (Mekinist) versus placebo in those with stage III melanoma with BRAF V600E or V600K mutations. Results statistically favored dabrafenib (Tafinlar) plus trametinib (Mekinist) compared to placebo.
- IX. Trametinib (Mekinist) was evaluated for efficacy in melanoma in those that had previously received BRAF inhibitor therapy. No patients achieved partial or complete response.
- X. Dabrafenib (Tafinlar) was evaluated as monotherapy for BRAF V600E mutation positive unresectable or metastatic melanoma in the BREAK-3 study. The open-label trial evaluated dabrafenib (Tafinlar) versus dacarbazine, which demonstrated a statistically significant increase in PFS compared to dacarbazine.
- XI. Dabrafenib (Tafinlar) was evaluated in the BREAK-MD study as a single-arm, Phase 2, open-label trial for mutation-positive melanoma, metastatic to the brain. The primary outcomes were ORR and DOR.
- XII. The COMBI-d study evaluated dabrafenib (Tafinlar) to trametinib (Mekinist) plus dabrafenib (Tafinlar) in first-line therapy for unresectable or metastatic BRAF V600E or V600K mutation-positive cutaneous melanoma. Overall survival was statistically in favor of combination therapy.
- XIII. The COMBI-v study evaluated dabrafenib (Tafinlar) plus trametinib (Mekinist) versus vemurafenib (Zelboraf) for BRAF V600E or V600K mutation-positive unresectable or metastatic melanoma, and overall survival data was statistically in favor of dabrafenib (Tafinlar) plus trametinib (Mekinist).
- XIV. Adjuvant therapy for melanoma that had lymph node involvement and was completely resected, therapy is authorized for a total of one year maximum. Safety and efficacy beyond this time frame has not been sufficiently established.
- XV. Dabrafenib (Tafinlar) was evaluated as monotherapy for BRAF V600E mutation positive unresectable or metastatic melanoma in the BREAK-3 study. The open-label trial evaluated dabrafenib (Tafinlar) versus dacarbazine, which demonstrated a statistically significant increase in PFS compared to dacarbazine.

Treatment of NSCLC

- XVI. A study of dabrafenib (Tafinlar) alone or administered with trametinib (Mekinist) was evaluated in an open-label, Phase 2 trial in subjects with BRAF V600E mutation-positive NSCLC. Combination therapy was statistically favored in overall response rate (ORR) and duration of response (DOR).
- XVII. Insight from oncology specialists indicate that the diagnosis of stage IV metastatic disease can include intra-pulmonary (disease contained within the lungs) and extra-pulmonary (disease spread to organs outside the lungs) metastases. Intra-pulmonary metastases are typically staged as M1a and described as one of the following situations: separate nodule in the other lung, pleural or pericardial nodules, or malignant pleural or pericardial effusions. The treatment

approach for those with intra-pulmonary metastases should be individualized and include surgery and, when surgery is not feasible, standard systemic therapy.

Treatment of Pediatric Low-Grade Glioma

- XVIII. In March of 2023 combination dabrafenib (Tafinlar) and trametinib (Mekinist) was FDA approved for pediatric patients 1 year of age and older with low-grade glioma (LGG) with a BRAF V600E mutation who require systemic therapy. Approval was based on results from the TADPOLE trial – a phase II/III open label trial comparing combination dabrafenib (Tafinlar)/trametinib (Mekinist) to standard of care carboplatin/vincristine.
- XIX. Following the initial diagnostic work-up, surgery is the first treatment modality for almost 80% of all LGG patients. Where complete resection is possible and felt to be without great risk of morbidity then surgery should take place. Following surgery, follow-up and observation only, may be indicated.
- XX. Trial participants included those aged 1 to 17 with BRAF V600 mutation- positive LGG whose tumor was unresectable and who required first line systemic therapy. Randomization was 2:1 with a majority of patients being female (60%) and white (72%). Patients treated with dabrafenib plus trametinib (n = 73) achieved an overall response rate (ORR) of 46.6% (95% CI, 34.8%-58.6%) compared with 10.8% (95% CI, 3.0%-25.4%) for patients treated with carboplatin plus vincristine (n = 37; P < 0.001). Patients in the dabrafenib/trametinib arm experienced a median duration of response of 23.7 months (95% CI, 14.5-not estimable [NE]); this was NE (95% CI, 6.6-NE) in the carboplatin/vincristine arm. Median progression free survival was reported as 20.1 (95% CI, 12.8-NE) and 7.4 (95% CI, 3.6-11.8) in the dabrafenib/trametinib arm and carboplatin/vincristine arms respectively with a hazard ratio of 0.31 (0.17-0.55). The OS results at interim analysis did not reach statistical significance. ORR is not a direct measure of drug benefit and is not an optimal surrogate marker or predictor of long-term efficacy, morbidity, or mortality.

Investigational or Not Medically Necessary Uses

- I. Treatment after previous BRAF inhibitor therapy
 - A. Trametinib (Mekinist) did not show to have efficacy in a trial evaluating as second-line therapy after previous therapy with BRAF inhibitors.
- II. Safety and efficacy of trametinib (Mekinist) and/or dabrafenib (Tafinlar) has not been sufficiently evaluated for safety and/or efficacy in the following settings:
 - A. Erdheim Chester Disease
 - i. Only vemurafenib (Zelboraf) is FDA-approved for ECD with BRAF V600E mutation, though due to limited treatment options, other targeted therapies, such as trametinib (Mekinist) and dabrafenib (Tafinlar), are used off-label based on limited retrospective data.
 - B. Leukemias, lymphomas
 - C. Neurofibromatosis type 1 (NF1)
 - D. Unresectable or metastatic solid tumors
 - i. In May 2022, combination dabrafenib (Tafinlar) and trametinib (Mekinist) was approved via an accelerated approval pathway for the treatment of adult and pediatric patients 6 years of age and older with unresectable or metastatic solid

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BRAF V600E mutated tumors who have progressed following prior treatment and have no satisfactory alternative treatment options. Approval was based on results from three clinical trials, the Phase 2 ROAR (Rare Oncology Agnostic Research) basket study, Subprotocol H of the Phase 2 NCI-MATCH study, and Study X2101.

- ii. Subprotocol H of the NCI-MATCH Trial was an open-label, single-arm study of 29 participants with BRAFV^{600E/K/R/D} mutated solid tumors, lymphoma, or multiple myeloma whose disease had progressed on at least one standard therapy. The study combined multiple cancer types (16), most of which were represented as single cases. The primary outcome measure was objective response rate (ORR), which was observed in 37.9% of patients (90% CI, 22.9% to 54.9%; P< 0.001). Median progression free survival of 11.4 months and median duration of response of 21.1 months. Due to the study design, small sample size, and lack of endpoints correlated with validated clinical outcomes the applicability of this data for clinical decision making is limited.
- iii. The Rare Oncology Agnostic Research (ROAR) basket trial was designed to assess the activity and safety of dabrafenib plus trametinib combination treatment in patients with BRAFV600E-mutated rare cancers. Interim results from the biliary tract cancer and low-grade glioma/high-grade glioma cohorts have been released. Primary endpoints for each of the studies was objective response rate (ORR). For the biliary tract cohort ORR was met by investigator-assessment [51% (95% CI 36-37); 22 of 43 patients] but not independent reviewer-assessment [47% (95% CI 31-62); 20 of 43 patients]. Median PFS was 9 months and median overall survival was 14 months. For the glioma cohorts, investigator assessed ORR was 33% in high-grade glioma (32% in glioblastoma) and 69% in low-grade glioma. Similar response rates were reported by independent radiology review (high-grade glioma 31%; low-grade glioma 69%). Investigator and independent reviewer reported duration of response and median PFS widely differed in the high-grade and low-grade cohorts which causes questionability for the true duration or response and PFS.
- iv. Study X2101 was a four-part, phase I/IIa, multi-center, open label study in pediatric patients with refractory or recurrent tumors. Pharmacokinetic and pharmacodynamic parameters were reported. Additional study arms went on to trial combination treatment; however, only low-grade glioma (20 participants) and Langerhans cell histiocytosis (10 participants) were reported. Overall, this data gives general dosing information but does not necessarily give actionable clinical efficacy data when making clinical decisions in children.

E. Pediatric Low-Grade Glioma, second line systemic therapy

- i. Clinical trials for the pediatric low grade glioma population included only those with BRAF V600–mutant low-grade glioma with progressive disease following surgical excision or non-surgical candidates who needed to begin first systemic treatment because of a risk of neurological impairment with progression. Trametinib (Mekinist) and dabrafenib (Tafinlar) combination therapy after the first line systemic therapy setting has not been evaluated.

Appendix

I. Table 1: Recommended Dosage for TAFINLAR Tablets for Oral Suspension (Weight-based)

Body weight	Recommended dosage
8 to 9 kg	20 mg twice daily
10 to 13 kg	30 mg twice daily
14 to 17 kg	40 mg twice daily
18 to 21 kg	50 mg twice daily
22 to 25 kg	60 mg twice daily
26 to 29 kg	70 mg twice daily
30 to 33 kg	80 mg twice daily
34 to 37 kg	90 mg twice daily
38 to 41 kg	100 mg twice daily
42 to 45 kg	110 mg twice daily
46 to 50 kg	130 mg twice daily
≥ 51 kg	150 mg twice daily

II. Table 2: Recommended Dosage for TAFINLAR Capsules in Pediatric Patients (Weight-based)

Body weight	Recommended dosage
26 to 37 kg	75 mg orally twice daily
38 to 50 kg	100 mg orally twice daily
51 kg or greater	150 mg orally twice daily

III. Table 3: Recommended Dosage for MEKINIST for Oral Solution (Weight-based)

Body weight	Recommended dosage total volume of oral solution once daily (trametinib content)
8 kg	6 mL (0.3 mg)
9 kg	7 mL (0.35 mg)
10 kg	7 mL (0.35 mg)
11 kg	8 mL (0.4 mg)
12 to 13 kg	9 mL (0.45 mg)
14 to 17 kg	11 mL (0.55 mg)
18 to 21 kg	14 mL (0.7 mg)
22 to 25 kg	17 mL (0.85 mg)
26 to 29 kg	18 mL (0.9 mg)
30 to 33 kg	20 mL (1 mg)
34 to 37 kg	23 mL (1.15 mg)
38 to 41 kg	25 mL (1.25 mg)
42 to 45 kg	28 mL (1.4 mg)
46 to 50 kg	32 mL (1.6 mg)
≥ 51 kg	40 mL (2 mg)

IV. Table 4: Recommended Dosage for MEKINIST Tablets in Pediatric Patients (Weight-based)

Body weight	Recommended dosage
26 to 37 kg	1 mg orally once daily
38 to 50 kg	1.5 mg orally once daily
51 kg or greater	2 mg orally once daily

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy

Policy Name	Disease state
encorafenib (Braftovi) binimetinib (Mektovi)	Malignant melanoma, unresectable or metastatic, with BRAF V600E or V600K mutation, combination therapy
cobimetinib (Cotellic)	Unresectable or metastatic melanoma with a BRAF V600E or V600K mutation
vemurafenib (Zelboraf)	Unresectable or metastatic melanoma with a BRAF V600E mutation
	Erdheim-Chester Disease with a BRAF V600E mutation
selumetinib (Koselugo)	Neurofibromatosis type 1 (NF1)

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated QL table to include solution and soluble tablet formulations. Added BRAF mutated pediatric LGG indication to the initial review section with supporting evidence. Added appendix dosing tables for pediatric dosage forms.	10/2023
Updated QL table, renewal criteria, and related policies to align with standard formatting. Divided supporting evidence per indication. Added NF1 and unresectable or metastatic solid tumors to E/I section. Removed specialist requirement upon renewal	10/2022
Added supporting evidence around stage IV metastatic disease and metastases.	10/2021
Criteria transitioned to policy, medications combined into one policy, addition of specialty prescriber, age edit, clarification on previous or alternative therapies to be considered for thyroid cancer. Quantity level limits updated.	11/2018
Criteria updated to include new indications of NSCLC and anaplastic thyroid cancer.	06/2018
Previous Reviews	11/2013
	01/2015

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP018

Description

Deflazacort (Emflaza) is a corticosteroid prodrug and vamorolone (Agamree) is a dissociative corticosteroid that suppresses the inflammatory pathway. Givinostat (Duvyzat) is a histone deacetylase (HDAC) inhibitor that inhibits HDAC pathological overactivity that results in the cascade of events leading to muscle damage, thereby counteracting the disease pathology, and slowing down muscle deterioration. Ataluren (Translarna) is a nonsense mutation targeting small molecule that bypasses inappropriate stop codons during dystrophin transcription.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
generic deflazacort	Duchenne Muscular Dystrophy (DMD)	6 mg tablets	0.9 mg/kg/day (round to nearest tablet size)
		18 mg tablets	
		30 mg tablets	
		36 mg tablets	
22.75 mg/mL oral suspension		0.9 mg/kg/day (see appendix)	
deflazacort (Brand Emflaza)		6 mg tablets	0.9 mg/kg/day (round to nearest tablet size)
		18 mg tablets	
		30 mg tablets	
		36 mg tablets	
22.75 mg/mL oral suspension		0.9 mg/kg/day (see appendix)	
vamorolone (Agamree)	40 mg/mL oral suspension	225 mL/30 days	
givinostat (Duvyzat)	8.86 mg/mL oral suspension	Weight based (see appendix)	
ataluren (Translarna)	Nonsense Mutation Duchenne Muscular Dystrophy (DMD)	TBD	40 mg/kg/day

Initial Evaluation

- I. **Generic deflazacort, deflazacort (Brand Emflaza) and vamorolone (Agamree)** may be considered medically necessary when the following criteria below are met:
 - A. Medication is prescribed by, or in consultation with, a neuromuscular specialist or neurologist; **AND**
 - B. Must not be used in combination with each other for treatment of Duchenne Muscular Dystrophy (DMD); **AND**
 - C. A diagnosis of **Duchenne Muscular Dystrophy (DMD)** when the following are met:
 1. Documentation of Duchenne Muscular Dystrophy (DMD) gene mutation; **OR**
 - i. Documentation of total absence of dystrophin confirmed by muscle biopsy; **AND**
 2. Member is two years or older; **AND**
 3. Member displays delayed motor milestones (e.g., child not walking by 18 months, toe walking, poor head control, not running by three years old, struggling to hop, abnormal gait, difficulty ambulating without assistance, etc.); **AND**
 - D. Member's current weight is documented; **AND**
 - E. Treatment with oral prednisone for six months or greater has been ineffective, not tolerated, or contraindicated; **AND**
 - F. Treatment with generic deflazacort has been ineffective, not tolerated, or contraindicated
- II. **Givinostat (Duvyzat)** is considered medically necessary when the following criteria below are met:
 - A. Member is six years or older; **AND**
 - B. Medication is prescribed by, or in consultation with, a neuromuscular specialist or neurologist; **AND**
 - C. Medication will not be used in combination with a dystrophin restoration treatment for Duchenne Muscular Dystrophy (e.g., ataluren (Translarna), Eteplirsen (Exondys 51), Golodirsen (Vyondys 53), Viltolarsen (Viltepso), Casimersen (Amondys 45), delandistrogene moxeparvovec-rokl (Elevidys)); **AND**
 - D. A diagnosis of **Duchenne Muscular Dystrophy (DMD)** when the following are met:
 1. Documentation of Duchenne Muscular Dystrophy (DMD) gene mutation; **OR**
 - i. Documentation of total absence of dystrophin confirmed by muscle biopsy; **AND**
 2. Member displays delayed motor milestones (e.g., child not walking by 18 months, toe walking, poor head control, not running by three years old, struggling to hop, abnormal gait, difficulty ambulating without assistance, etc.); **AND**
 - E. Member must be ambulatory (e.g., able to walk); **AND**
 - F. Member is using a corticosteroid concomitantly with givinostat (Duvyzat); **OR**
 1. Treatment with a corticosteroid for six months or greater has been ineffective, not tolerated, or contraindicated; **AND**
 - G. Member's current weight is documented; **AND**
- III. **Ataluren (Translarna)** is considered medically necessary when the following criteria below are met:

- A. Member is five years or older; **AND**
 - B. Medication is prescribed by, or in consultation with, a neuromuscular specialist or neurologist; **AND**
 - C. Medication will not be used in combination with givinostat (Duvyzat) or a dystrophin restoration treatment for Duchenne Muscular Dystrophy [e.g., Eteplirsén (Exondys 51), Golodirsén (Vyondys 53), Viltolarsén (Viltepso), Casimersén (Amondys 45), delandistrogene moxeparvovec-rokl (Elevidys)]; **AND**
 - D. A diagnosis of **nonsense mutation Duchenne Muscular Dystrophy (DMD)** when the following are met:
 - 1. Documentation of Duchenne Muscular Dystrophy (DMD) gene mutation; **AND**
 - 2. Documentation of nonsense mutation; **AND**
 - 3. Member displays delayed motor milestones (e.g., child not walking by 18 months, toe walking, poor head control, not running by three years old, struggling to hop, abnormal gait, difficulty ambulating without assistance, etc.); **AND**
 - E. Member must be ambulatory (e.g., able to walk); **AND**
 - F. Member is using a corticosteroid concomitantly with ataluren (Translarna); **OR**
 - 1. Treatment with a corticosteroid for six months or greater has been ineffective, not tolerated, or contraindicated; **AND**
 - G. Member's current weight is documented
- IV. Deflazacort (Emflaza), vamorolone (Agamree), givinostat (Duvyzat), and ataluren (Translarna) are considered investigational when used for all other conditions, including, but not limited to:
- A. Dysferlinopathies: including Miyoshi Myopathy (MM) and limb girdle muscular dystrophy type 2B (LGMD2B)
 - B. Ulcerative Colitis
 - C. Myelodysplastic Syndromes: Polycythemia vera
 - D. Becker muscular dystrophy (BMD)
 - E. Cystic fibrosis

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Treatment provides clinical benefit to the member, defined as slow or stabilize disease progression in net motor function, compared to pretreatment baseline [e.g., stability or improvement in gait, muscle strength, slowed rate of decline in timed function tests (e.g., 6MWT, 4SC, NSAA, etc.)]; **AND**
- IV. The request is for **generic deflazacort, deflazacort (Brand Emflaza), or vamorolone (Agamree); AND**
 - Medication requested will not be used in combination with another corticosteroid (e.g., prednisone, deflazacort, etc.); **OR**
- V. The request is for **givinostat (Duvyzat); AND**

- Member must be ambulatory (e.g., able to walk); **AND**
 - Medication will not be used in combination with a dystrophin restoration treatment for Duchenne Muscular Dystrophy (e.g., Eteplirsen (Exondys 51), Golodirsen (Vyondys 53), Viltolarsen (Viltepso), Casimersen (Amondys 45), delandistrogene moxeparvovec-rokl (Elevidys)); **AND**
 - The medication will be used in combination with a steroid unless contraindicated or not tolerated; **OR**
- VI. The request is for **ataluren (Translarna)**; **AND**
- Member must be ambulatory (e.g., able to walk); **AND**
 - Medication will not be used in combination with givinostat (Duvyzat) or a dystrophin restoration treatment for Duchenne Muscular Dystrophy (e.g., Eteplirsen (Exondys 51), Golodirsen (Vyondys 53), Viltolarsen (Viltepso), Casimersen (Amondys 45), delandistrogene moxeparvovec-rokl (Elevidys)); **AND**
 - The medication will be used in combination with a steroid unless contraindicated or not tolerated

Supporting Evidence

- I. DMD (Duchenne Muscular Dystrophy) is a rare X-linked genetic disorder characterized by progressive muscle degeneration and weakness due to alterations in DMD genes required to synthesize a protein called dystrophin. Dystrophin is a major component of the cytoskeleton structure that prevents contraction-induced damage. Muscles with low levels of dystrophin are more sensitive to damage, resulting in progressive muscle loss and function. Duchenne Muscular Dystrophy initially presents as developmental delay and weakness in proximal limb muscle in young males ages three to five years old. Although rare, DMD may affect girls. Due to its gradual progression, if left untreated, most patients with DMD will lose ambulation before the age of 12 years and require non-invasive ventilation. Treatments in DMD target improving motor function and delaying the onset of cardiac and respiratory complications. Given the rarity and complexity of diagnosis and management of DMD, the treatment of DMD must be initiated by, or in consultation with, a neurologist or neuromuscular specialist.
- II. Suspected cases of DMD should be referred to a neuromuscular specialist to evaluate creatinine kinase levels. If these are elevated, the diagnosis of DMD should be confirmed by dystrophin genetic testing. In rare cases genetic testing may be negative, but a diagnosis can still be confirmed by a muscle biopsy and dystrophin analysis.
- III. There are no curative therapies for DMD. Supportive care is crucial for optimizing health and quality of life for patients with DMD. The 2018 DMD Care Considerations Working Group Diagnosis and Management of Duchenne Muscular Dystrophy guidelines note that glucocorticoids may be used to improve physical functioning and should be started prior to substantial physical decline. Prednisone and deflazacort have been shown to improve motor and pulmonary function and improve survival. Guidelines have not been updated to include vamorolone (Agamree) or givinostat (Duvyzat).
- IV. There are five gene-based therapies FDA-approved to treat patients with DMD: eteplirsen (Exondys 51), golodirsen (Vyondys 53), viltolarsen (Viltepso), casimersen (Amondys 45), and delandistrogene moxeparvovec-rokl (Elevidys). The accelerated approval of all five drugs was based on the surrogate endpoint of an increase in dystrophin production in the skeletal muscle observed in some patients treated with the drugs. However, the amount of dystrophin expression to be translated into a clinical benefit has yet to be established in patients with DMD.

deflazacort (Emflaza)

- V. Deflazacort (Emflaza) was evaluated in two multicenter, randomized, double-blind, placebo-controlled trials in 225 patients. Study 1 consisted of 196 male pediatric patients, five to 15 years of age with documented mutation of the dystrophin gene, and onset of weakness before five years of age. The primary endpoint was the average change in muscle strength score between baseline and week 12. The average change was 0.15 (95% CI 0.01, 0.28) and -0.10 (95% CI -0.23, 0.03) for the deflazacort (Emflaza) and placebo groups, respectively. Study 2 consisted of 29 male pediatric patients, six to 12 years of age with documented mutation of the dystrophin gene. The primary endpoint was the average muscle strength score at two years. The results were not statistically significant.

vamorolone (Agamree)

- VI. Vamorolone (Agamree) is an FDA approved dissociative steroid indicated for treatment of DMD. Vamorolone (Agamree) is available as a 40mg/mL suspension and dosing is weight-based. Per label, the recommended dose of vamorolone (Agamree) is 6mg/kg, with a max of 300mg daily for those >50kg. A dissociative steroid retains a selective anti-inflammatory profile and assumed to have a favorable side effect profile compared to traditional corticosteroids with reduced bone fragility, metabolic disturbance, and immune suppression.
- VII. Vamorolone (Agamree) was studied in a Phase IIb, multicenter, double-blinded, randomized, placebo- and prednisone-controlled trial (VISION-DMD phase IIb) in 121 boys ages ≥ 4 years and <7 years old with confirmed DMD via DMD gene mutation or muscle biopsy. Participants were randomized to receive low or high dose vamorolone (2mg/kg [N=30] or 6mg/kg [N=30]), prednisone (0.75mg/kg [N=30]) or placebo (N=31) daily. Patients that received prior treatment with oral glucocorticoids or other immunosuppressants or clinically significant cardiac disease were excluded. Baseline characteristics were similar between all groups with a mean age of 5.4 years, weight of 20kg, 82.9% Caucasian, and baseline time to stand (TTSTAND) velocity of 1.7m/s.
- VIII. The primary endpoint was TTSTAND from supine velocity in the vamorolone 6 mg/kg per day group vs placebo. Treatment with vamorolone 6 mg/kg/day resulted in statistically significant lower TTSTAND scores relative to placebo at week 24, least square mean (LSM) 0.05 m/s in high dose vamorolone compared to -0.01 m/s in the placebo group, LSM difference 0.06m/s, $p=0.002$ (95% CI, 0.02-0.10). Secondary endpoints included TTSAND velocity in the vamorolone 2mg/kg per day group vs placebo, 6-minute walk test (6MWT) and time to run/walk (TTRW) between high dose vamorolone compared to placebo and low dose vamorolone compared to placebo.
- TTSTAND velocity in the vamorolone 2mg/kg per day 0.03 m/s vs placebo -0.01 m/s, LSM difference 0.05 m/s, $p=0.02$ (95% CI, 0.01-0.08)
 - i. TTSTAND is a validated outcome measure for DMD. A difference of 0.05 m/s in TTSTAND velocity is indicative of clinically meaningful changes. Strength testing is reliable and reflects differences between steroid-treated and naive populations between the ages of 4 and 9 years and for stronger and more mobile subpopulations aged 10 and older. However, strength testing has limited continuity across the entire age range of affected individuals from young children to adults.
 - 6MWT in the vamorolone 6mg/kg per day 28.3m vs placebo -13.3m LSM difference 41.6m, $p=0.003$ (95% CI, 14.2-68.9); vamorolone 2mg/kg per day 23.9 m vs placebo -13.3m, LSM difference 37.1, $p=0.009$ (95% CI, 9.6-64.7)
 - TTRW velocity in the vamorolone 6mg/kg per day 0.26m/s vs placebo 0.01m/s LSM difference 0.024 m/s, $p=0.024$ (95% CI, 0.09-0.39); vamorolone 2mg/kg per day 0.16 m/s vs placebo 0.01 m/s, LSM difference 0.02 m/s, $p>0.05$ (95% CI, -0.03-0.28)

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- IX. The number of participants reporting at least one adverse event (AE) was similar between all groups. Participants in the prednisone group experienced linear growth delay, which was not present in the vamorolone group. There were two treatment-emergent vertebral fractures at week 24; one participant in the prednisone group had a total of four incident vertebral fractures, and one participant in the placebo group had a single incident vertebral fracture.
- X. The FDA-label for vamorolone (Agamree) has similar warnings and precautions as prednisone and deflazacort (Emflaza). These glucocorticoids have similar safety and efficacy profiles and requiring step through prednisone and generic deflazacort is both clinically appropriate and cost-effective.
- XI. Additionally, 41 participants enrolled in a 30-month open label extension trial. Participants were matched and compared with participants from the DNHS. Participants in DNHS were first eligible for inclusion in the control group after they had experienced 6 months of continuous glucocorticoid exposure. There was a decrease in mean TTSTAND velocity from baseline to 30 months (0.206 rises/s vs 0.189 rises/s), which was not a statistically significant change (–0.011 rises/s; CI, –0.068 to 0.046 rises/s). There were no statistically significant differences between participants receiving high dose vamorolone and matched participants in the historical control groups receiving glucocorticoid treatment.
- XII. The clinical program for vamorolone (Agamree) consisted of a moderate to well-designed randomized clinical trial reporting consistent improvement in TTSTAND score, which is an objective, validated measure of muscular function in DMD. Milestones of disease progression, such as loss of ability to rise from floor, ambulate 10 m and self-feed occur in a predictable order, and loss of those abilities can be predicted by timed functional evaluations. The generalizability of current clinical data may be limited due to the exclusion of patients with severe disease. However, in the absence of substantial physical decline, vamorolone (Agamree) may provide potential clinical benefit similar to standard of care glucocorticoids.

givinostat (Duvyzat)

- XIII. Givinostat (Duvyzat) is a histone deacetylase (HDAC) inhibitor, the first oral nonsteroidal drug FDA-approved for all genetic variants of DMD. Although the exact mechanism of HDACs in DMD is still unknown, it is thought that inhibiting HDAC overactivity prevents the cascade of events leading to muscle damage, stabilizing disease progression and slowing down muscle deterioration.
- XIV. Givinostat (Duvyzat) was evaluated in a randomized, double blind, placebo controlled, multicenter Phase 3 clinical trial (EPIDYS; NCT02851797). The trial enrolled 179 ambulant boys six years of age or older with confirmed DMD and on stable doses of systemic corticosteroids to receive weight-based dosing of givinostat (Duvyzat) or placebo for 18 months. The primary outcome assessed change from baseline in the time to climb 4 standard stairs (4SC) and was complemented by several key secondary endpoints: six-minute walk test (6MWT), North Star Ambulatory Assessment (NSAA), time to rise from floor (TTR), and fat fraction of the vastus lateralis (VL-MFF) measured by magnetic resonance spectroscopy (MRS) which have proven to be sensitive to disease progression in DMD and predictive of loss of ambulation.
- XV. The study met its primary endpoint, and treatment with givinostat (Duvyzat) showed a slower 4SC decline compared to placebo in change from baseline at 18 months (difference vs. placebo of -1.78 seconds, $p=0.037$). Additionally, secondary endpoints that evaluated muscle function and strength showed favorable results in the givinostat (Duvyzat) treated group. Givinostat (Duvyzat) treatment was associated with less decline in NSAA total score and item loss, which was nominally significant but not statistically significant, indicating givinostat (Duvyzat) potential to delay disease progression. Givinostat (Duvyzat) treated participants had a 30% reduction in

VLFF compared to the placebo, where VL-MFF is a predictor of loss of ambulation and indicates disease progression in DMD individuals.

- XVI. The clinical program for givinostat (Duvyzat) consisted of a moderate quality clinical trial reporting slowed progression in 4SC velocity, which is a validated measure of functional capability in ambulatory patients with DMD. The primary endpoint, 4SC velocity, is a validated endpoint in ambulatory patients where a clinically meaningful change is considered >1 second and a 1.6 second change correlates with a 3-year prolongation in ambulation. Additionally secondary endpoints favor givinostat (Duvyzat) vs placebo, further supporting efficacy. Timed functional evaluations correlate with milestones of disease progression, such as loss of ability to rise from floor, ambulation, and ability to self-feed. Givinostat (Duvyzat) provides a clinically meaningful change in physical function as evident in supporting secondary outcomes compared to placebo. An ongoing extension study (NCT03373968) is evaluating the long-term safety and efficacy of givinostat (Duvyzat).
- XVII. A greater number of participants in the givinostat (Duvyzat) group (69%) than placebo (28%) had adverse events related to treatment, including diarrhea, abdominal pain, vomiting, decreased platelet counts, and increase in triglycerides. Most adverse events were mild to moderate in severity and were managed by dose reduction or interruption. Vomiting was reported in two participants in the givinostat group as a severe adverse event. Majority of patients completed the study and treatment compliance was high in both groups. There are currently no contraindications to using givinostat (Duvyzat).

Ataluren (Translarna)

- VII. Ataluren (Translarna) is a nonsense mutation targeting small molecule pending FDA-approval for the treatment of nonsense mutation Duchenne Muscular Dystrophy (DMD). Ataluren (Translarna) was studied in a Phase III, double-blinded, randomized, placebo-controlled study (study 041) and an observational propensity-matched trial. Study 041 was prespecified to analyze a modified intent to treat population. However, after completion of the trial, no statistical difference was identified in the primary and secondary endpoints. The manufacturer then completed a secondary analysis of with all participants (ITT population) enrolled in Study 041.
- VIII. A total of 185 boys ages 5 years and older with confirmed nonsense mutation DMD were randomized to receive ataluren (Translarna) 40mg/kg/day, split into three doses, or placebo orally daily for 72 weeks. Concomitant corticosteroid use was permitted if the participant was stable on therapy before randomization and participants were required to be ambulatory. Baseline characteristics were similar between both cohorts with a mean age of 8 years, most participants had a mean baseline six-minute walking distance (6MWD) of >400 meters (41%), and all participants had prior exposure to corticosteroids. The primary endpoint was change in 6MWD in the intent to treat population, which was -53.0m in the ataluren (Translarna) group and -67.4m in the placebo arm, difference 14.4m, $p=0.0248$. Ataluren (Translarna) had a lesser decrease in NSAA total score compared to placebo (-3.7 vs -4.5, difference 0.9, $p=0.0235$) and time to climb 4 stairs (4.98 seconds vs 6.04 seconds, difference -1.06, $p=0.0078$).
- IX. Additionally, 298 participants were enrolled in an observational extension trial. Participants were continued on ataluren (Translarna) plus standard of care treatment and followed for at least 5 years or until study withdrawal and matched and compared to participants on standard of care treatment from the Duchenne Natural History Study. After a mean duration of treatment of 67 months, participants receiving ataluren (Translarna) plus standard of care demonstrated a significant delay in the median age at loss of ambulation compared natural history data matches receiving standard of care alone (16.5 yrs vs 13.0 yrs, HR 0.455, $p<0.0001$). Interim results also suggest a trend toward a delay in worsening of pulmonary function (median age at FVC <60%

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was 17.7 years in those treated with ataluren (Translarna) compared to 15.6 years in the natural history comparator (HR = 0.63, p=0.0086). The observational study demonstrated that participants on ataluren plus standard of care loss ambulation at a later age compared to propensity matched participants on standard of care in a natural history database and patients that remained on therapy did not have any new safety concerns.

- The secondary analysis demonstrated that the change in 6MWD was significantly less in the ataluren group compared to placebo (difference of 14.4 m, p=0.0248). The difference between both arms did not meet the minimal clinically important difference of 28.5 m and the difference is not considered clinically significant. Additionally, changing the targeted population after completion of the trial significantly compromises the integrity of the trial.

- XVIII. The rate of treatment emergent adverse events was similar between ataluren (Translarna) and placebo (85.3% vs 84.7%). The most common adverse events include vomiting, upper respiratory tract infection, nasopharyngitis, headache, and fall. No participants discontinued therapy due to treatment emergent adverse events.
- XIX. Exposure to treatment with dystrophin restoration agents for DMD (e.g., ataluren (Translarna), eteplirsen (Exondys 51), golodirsen (Vyondys 53), viltolarsen (Viltepso), casimersen (Amondys 45), delandistrogene moxeparvovec-rokl (Elevidys) etc.) was excluded from the EPIDYS trial. Exposure to treatment with givinostat (Duvyzat) and dystrophin restoration agents for DMD was excluded from Study 041, and the efficacy and safety of combination treatment with ataluren (Translarna) has not been evaluated.
- XX. Optimal sequencing of DMD gene therapies and use of givinostat (Duvyzat) has not been evaluated. Givinostat (Duvyzat) is not limited to use in any specific DMD variant and could potentially be used in most patients with DMD, including those that previously received gene therapies.

Appendix

I. Table 1. Recommended dosing of givinostat (Duvyzat)

Weight (kg)	Dosage	Oral suspension volume	Volume per day supply	# bottles per day supply
10 – 19 kg	2.22 mg twice daily	2.5 mL twice daily	140 mL/28 days	1 bottle/28 days
20 – 39 kg	31 mg twice daily	3.5 mL twice daily	140 mL/20 days	1 bottle/20 days
40 – 59 kg	44.3 mg twice daily	5 mL twice daily	280 mL/28 days	2 bottles/28 days
> 60 kg	53.2 mg twice daily	6 mL twice daily	280 mL/23 days	2 bottles/23 days

- Givinostat (Duvyzat) is available as an 140 mL oral suspension, containing 8.86 mg givinostat per mL. The recommended dosage of givinostat (Duvyzat) is based on body weight and administered orally twice daily with food
- Adverse reactions caused by givinostat (Duvyzat) may necessitate a dosagemodification and/or dosage interruption.

II. Table 2. Recommended dosing of vamorolone (Skyclarys)

Weight (kg)	Dosage	Oral suspension volume	Volume per 28-day supply	# bottles per day supply
10 – 19 kg	114 mg once daily	3 mL once daily	84 mL	1 bottle/33 days
20 – 39 kg	234 mg once daily	6 mL mg once daily	168 mL	1 bottle/16 days
40 – 45 kg	270 mg once daily	6.75 mL once daily	190 mL	2 bottles/29 days
> 46 kg	300 mg once daily	7.5 mg once daily	210 mL	2 bottles/26 days

- Vamorolone (Agamree) is available as an 100mL oral solution, containing 40mg of vamorolone per mL.
- The recommended dose of vamorolone (Agamree) is 6 mg/kg taken orally once daily, up to a maximum daily dosage of 300 mg for members weighing more than 50 kg (110 lb)

III. **Table 3. Recommended dosing of deflazacort (Emflaza)**

Weight (kg)	Dosage	Oral suspension volume	Volume per 28-day supply	# bottles per day supply
10 – 19 kg	17 mg once daily	0.75 mL once daily	21 mL	2 bottle/34 days
20 – 39 kg	35 mg once daily	1.6 mL mL once daily	45 mL	4 bottles/32 days
40 – 59 kg	53 mg once daily	2.4 mL once daily	68 mL	5 bottles/27 days
> 60 kg	63 mg once daily	2.8 mg once daily	79 mL	6 bottles/27 days

- Deflazacort is available as a 13mL oral solution, containing 22.75mg of deflazacort per mL.
- The recommended dose of deflazacort is weight based, 0.9 mg/kg, and taken orally once daily. In patients who experience intolerable adverse effects, may decrease the dose by 25% to 33%.

Investigational or Not Medically Necessary Uses

- I. Dysferlinopathies: including Miyoshi Myopathy (MM) and limb girdle muscular dystrophy type 2B (LGMD2B)
 - A. Deflazacort as an ineffective therapy in dysferlinopathies was shown in a double-blinded, placebo-controlled trial. Further evaluation is needed to support use of deflazacort (Emflaza) in this setting.
- II. Vamorolone (Agamree) has not been FDA-approved, or sufficiently studied for safety and efficacy for Ulcerative Colitis
 - A. There is a withdrawn phase I/II study evaluating the use of vamorolone in pediatric ulcerative colitis.
- III. Myelodysplastic Syndromes: Polycythemia vera (PV)
 - A. Givinostat is currently being studied for the treatment of PV. Results from a phase 1/2 study in 51 patients demonstrated an overall response rate of over 80% throughout a four-year follow-up period and an acceptable safety profile; however further evaluation is needed to support the use of givinostat (Duvyzat) in this setting.
- IV. Becker muscular dystrophy (BMD)
 - A. A phase 2 study evaluating givinostat in patients with BMD failed to show significant difference in the primary endpoint compared with placebo. Additionally, treatment with givinostat did not differ in strength assessments or timed-function tests. Givinostat showed a potential signal in slowing progression of BMD via MRI assessment; however, MRI results evaluating disease progression in BMD have yet to be translated into a clinical benefit.
- V. Cystic fibrosis
 - A. Ataluren was an investigational therapy for CF caused by nonsense mutations, which prevent the production of a normal cystic fibrosis transmembrane conductance regulator (CFTR) protein. A dysfunctional or nonexistent CFTR protein disrupts the salt and water

balance in the lungs and other tissues and leads to the thick, sticky mucus associated with cystic fibrosis. Phase 3 data did not show significant improvement in lung function or enough of a decrease in exacerbations and development in this space has ceased.

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Related Policies

Currently there are no related policies.

Policy Implementation/Update

Action and Summary of Changes	Date
Added criteria for new medication, ataluren (Translarna). Updated QL table, supporting evidence, removed 2016 American Academy of Neurology Recommendations on Corticosteroids in the supporting evidence as the guidelines are retired as of 2/2025.	7/2025
Added ambulatory requirement in renewal. Updated supporting evidence at QL table.	07/2024
Renamed deflazacort and vamorolone policy to "Treatments for Duchenne muscular dystrophy" policy. Added criteria for new medication, givinostat (Duvyzat). Updated QL table, supporting evidence, E/I section, references. Added appendix and related policies.	05/2024
Added step therapy requirement through generic deflazacort for brand vamorolone (Agamree) and brand deflazacort (Emflaza) and updated supporting evidence to reflect required step therapy.	02/2024
Realigned QL table and placed dosage form next to quantity limit. Added vamorolone to QL table Updated initial evaluation to include muscle biopsy and clinical features for diagnosis of DMD. Added vamorolone criteria and investigational condition. Updated supporting evidence.	11/2023
Updated initial approval duration to six months, and QLL box with weight-based dosing. Added requirement for neuromuscular specialist or neurologist. Included requirement for confirmation of diagnosis by genetic testing and addition of member weight to confirm dosing. Requires prednisone be tried and failed for six months to be deemed ineffective or have intolerance. Updated renewal criteria to include requirement for previous approval by Moda and not allowing establishing therapy with samples. Added examples of symptom improvement to renewal criteria.	05/2020
Revised to policy format, include use in pediatric patients down to two years of age.	07/2019
Update to criteria	01/2017
Criteria creation	05/2017

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP142

Description

Lonsurf combines trifluridine and tipiracil. Trifluridine is an orally administered nucleoside analog that is incorporated into DNA to interfere with DNA synthesis and proliferation; while, tipiracil increases exposure to trifluridine by inhibiting thymidine phosphorylase.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
trifluridine/tipiracil (Lonsurf)	Stomach or esophagogastric adenocarcinoma – metastatic, previously treated	15 mg/6.14 mg tablets	80 tablets/28 days
	Colorectal cancer – metastatic, previously treated	20 mg/8.19 mg tablets	80 tablets/28 days

Initial Evaluation

- I. **Trifluridine/tipiracil (Lonsurf)** may be considered medically necessary when the following criteria below are met:
 - A. The member is 18 years of age or older; **AND**
 - B. The medication is prescribed by, or in consultation with, an oncologist or a gastroenterologist; **AND**
 - C. A diagnosis of one of the following:
 1. **Colorectal cancer; AND**
 - i. The disease is metastatic (i.e., stage IV); **AND**
 - ii. The member has been previously treated with a fluoropyrimidine (e.g., fluorouracil, capecitabine, S-1), oxaliplatin, and irinotecan-based chemotherapy; **AND**
 - iii. The tumor has been tested and is documented to be KRAS mutant-type; **OR**
 - a. The tumor has been tested and is documented to be KRAS wild-type; **AND**
 - i. The member has been previously treated with an anti-EGFR therapy (e.g., cetuximab, panitumumab); **AND**
 - iv. Trifluridine/tipiracil (Lonsurf) will be used as monotherapy; **OR**
 - a. Trifluridine/tipiracil (Lonsurf) will be used in combination with an anti-VEGF biological therapy (e.g., bevacizumab); **OR**

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2. **Gastric or gastroesophageal junction adenocarcinoma; AND**
 - i. The disease is metastatic (i.e., stage IV); **AND**
 - ii. The member has received at least two prior lines of chemotherapy that have included a fluoropyrimidine (e.g., fluorouracil, capecitabine, S-1), a platinum therapy (e.g., cisplatin, carboplatin, oxaliplatin), and one of the following: a taxane (e.g., docetaxel, paclitaxel) or irinotecan; **AND**
 - iii. The tumor is HER2- overexpression negative (HER2-negative); **OR**
 - a. The tumor is HER2- overexpression positive (HER-2 positive); **AND**
 - i. The member has received prior HER2/neu-targeted therapy (e.g., trastuzumab); **AND**
 - iv. Provider attests that trifluridine/tipiracil (Lonsurf) is being requested as a third-line or subsequent therapy; **AND**
 - v. Trifluridine/tipiracil (Lonsurf) will be used as monotherapy
- II. Trifluridine/tipiracil (Lonsurf) is considered investigational when used for all other conditions, including but not limited to:
 - A. Combination therapy with other oncolytic agents not outlined above
 - B. Colorectal, gastric, or gastroesophageal cancer at a dose <20 mg/m² orally twice daily
 - C. Non adenocarcinoma gastric or gastroesophageal junction (e.g., squamous cell type)
 - D. Gastric or gastroesophageal junction adenocarcinoma prior to at least two previous lines of chemotherapy and prior to use of all of the following: a fluoropyrimidine, a platinum therapy, and one of the following – taxane or irinotecan
 - E. Biliary track cancers
 - F. Tumors that are not colorectal, gastric or gastroesophageal in nature

Renewal Evaluation

- I. Member has a previous prior authorization approval for this agent through this health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Documentation of member's current body surface area is provided in meters squared; **AND**
- IV. Trifluridine/tipiracil (Lonsurf) is being used at or above a dose of 20 mg/m²; **AND**
- V. The member has not experienced disease progression while on trifluridine/tipiracil (Lonsurf); **OR**
 - Documentation of compelling clinical evidence of benefit is provided if therapy is to be continued in the setting of progression.

Supporting Evidence

- I. Trifluridine is an orally administered nucleoside analog that is incorporated into DNA to interfere with DNA synthesis and proliferation, and tipiracil increases exposure to trifluridine by inhibiting thymidine phosphorylase. The clinical trials for FDA-approval of trifluridine/tipiracil (Lonsurf) were in patients 18 years and older; therefore, there is a lack of safety and efficacy data from clinical trials for use in pediatric patients.
- II. Many treatment options exist for the conditions listed in this policy. Initial and next line therapies in these settings is contingent upon patient specific characteristics. Given the complexities surrounding diagnosis and treatment choices, targeted drug therapies should be prescribed by, or in consultation with, a specialist.
- III. Pivotal clinical trials for FDA-approved indications evaluated safety and efficacy of trifluridine/tipiracil (Lonsurf) as monotherapy in heavily pretreated patients. The therapies listed in the above criteria had been tried and failed by the majority of patients enrolled in the clinical trials.
- IV. **Colorectal Cancer (CRC)**
 - The safety of LONSURF was evaluated in RECURSE, a randomized (2:1), double-blind, placebo-controlled trial in patients with previously treated metastatic colorectal cancer. Patients had received at least 2 prior regimens of standard chemotherapy and were refractory to, or failing, all of the following within three months: Fluoropyrimidine, irinotecan and oxaliplatin, anti-VEGF biologic therapy, anti-EGFR therapy (if *RAS* wild type). Eight hundred total patients were enrolled and received LONSURF 35 mg/m²/dose (n=533) or placebo (n=265) twice daily on Days 1 through 5 and Days 8 through 12 of each 28-day cycle. The primary outcome was overall survival (OS) measured every 8 weeks until defined endpoint. Secondary outcome measures were progression-free survival (PRS) and percentage of patients with adverse events. The median OS improved from 5.3 months with placebo to 7.1 months with LONSURF, and the hazard ratio for death in the LONSURF group versus the placebo group was 0.68 (95% confidence interval [CI], 0.58 to 0.81; P<0.001).
 - Currently, trifluridine/tipiracil (Lonsurf) is approved by the FDA for use in monotherapy in both metastatic gastric cancer and metastatic colorectal cancer, mCRC. The NCCN revised their opinion on this for the mCRC guidelines allowing therapy with bevacizumab in combination with trifluridine/tipiracil (Lonsurf) versus requiring failure of bevacizumab first or requiring trifluridine/tipiracil (Lonsurf) to be used as monotherapy. The panel had this decision from a review of the following information: A phase I single-arm, open label study (C-TASK FORCE) where all patients (n=25) enrolled were refractory/intolerant to fluoropyrimidine, irinotecan, oxaliplatin, anti-VEGF therapy, and anti-EGFR therapy (if wild-type *KRAS*). The endpoint was PFS at 16 weeks which was 42.9%. Based on this information, a Danish phase II trial was done with 93 mCRC patients comparing trifluridine/tipiracil (Lonsurf) with and without bevacizumab. After a median follow-up of 10 months, the median PFS (primary endpoint) was 2.6 months for trifluridine/tipiracil (Lonsurf) alone compared to 4.6 months in combination with bevacizumab (HR, 0.45; 95% CI, 0.29-0.72; P = .0015). A retrospective study of 57 patients with refractory mCRC showed similar results, with an improved median OS for trifluridine/tipiracil (Lonsurf) with bevacizumab versus without (14.4 months vs. 4.5 months; P < .001).

Based on this data, the panel added +/- use of bevacizumab as a treatment option for patients progressing through standard therapies. This same treatment is currently being evaluated in a phase III trial, SUNLIGHT, due for completion in 2023.

V. Gastric or gastroesophageal junction adenocarcinoma

- The safety of LONSURF was evaluated in TAGS, an international, randomized (2:1), double blind, placebo-controlled trial in patients with metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma who were previously treated with at least 2 prior chemotherapy regimens for advanced disease. Previous treatments must have included a fluoropyrimidine, a platinum, and either a taxane or irinotecan. Patients with HER2/neu-positive tumors must have received prior HER2/neu-targeted therapy, if available. Adjuvant chemotherapy could be counted as one prior regimen in patients who had recurrence during or within 6 months of completion of the adjuvant chemotherapy. Five hundred and seven total patients received either LONSURF 35 mg/m² /dose (n=335) or placebo (n=168) twice daily on Days 1 through 5 and Days 8 through 12 of each 28-day cycle with best supportive care. The primary outcome was OS and secondary outcomes were PFS and adverse events. Median overall survival was 5.7 months (95% CI 4.8-6.2) in the trifluridine/tipiracil (Lonsurf) group and 3.6 months (3.1-4.1) in the placebo group (hazard ratio 0.69 [95% CI 0.56-0.85]; one-sided p=0.00029, two-sided p=0.00058). Presently, molecular testing for HER2 status, microsatellite instability status, and PD-L1 expression are used in the clinical management of locally advanced, unresectable, and metastatic EGJ cancers. HER2 testing is recommended for all patients with esophageal or EGJ cancer at the time of diagnosis if metastatic disease is documented or suspected.
- There is no globally accepted standard for first-line treatment of HER2/neu negative gastric or gastroesophageal adenocarcinoma. When these indications were added to the policy, NCCN guidelines were not updated to provide recommendations for this agent. Clinical trial experience with extensive patient treatment history is the basis for addition into the policy.

- VI. The recommended dosage for trifluridine/tipiracil (Lonsurf) is 35mg/m²/dose orally twice a day; however, due to the medication's adverse events, dose decreases are common and from the package insert, a maximum of 3 dose reductions are permitted. It is recommended to permanently discontinue trifluridine/tipiracil (Lonsurf) in patients who are unable to tolerate a dose of 20 mg/m² orally twice daily and to not escalate dosage after it has been reduced. There is one exception to the 20mg/m² and that is those with severe renal impairment (CrCl 15-29), who can go to 15mg/m² and then should discontinue if unable to be tolerated.

Investigational or Not Medically Necessary Uses

All indications listed below have not been sufficiently studied for safety and efficacy, or have inconclusive evidence regarding safety and efficacy for use of trifluridine/tipiracil (Lonsurf).

- I. Combination therapy with other oncolytic agents
- II. Colorectal cancer prior to the metastatic setting, and/or prior to use of a fluoropyrimidine, oxaliplatin, and irinotecan-based chemotherapy regimen, and/or prior to use of an anti-

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- VEGF biological therapy, and/or if the member is KRAS mutant-type use prior to an anti-EGFR therapy
- III. Colorectal, gastric, or gastroesophageal cancer at a dose < 20 mg/m² orally twice daily
 - IV. Non adenocarcinoma gastric or gastroesophageal junction (e.g., squamous cell type)
 - V. Gastric or gastroesophageal junction adenocarcinoma prior to at least two previous lines of chemotherapy and prior to use of all of the following: a fluoropyrimidine, a platinum therapy, and one of the following – taxane or irinotecan
 - VI. Biliary track cancers
 - VII. Tumors that are not colorectal, gastric, or gastroesophageal in nature

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
regorafenib (Stivarga)	Colorectal Cancer
encorafenib (Braftovi)	

Policy Implementation/Update:

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Action and Summary of Changes	Date
Reformatted existing policy to match current standards. Updated renewal section to match requirements across other anti-cancer policies. Reviewed and updated references for building a better supportive evidence section. Included addition under mCRC for combination use with Avastin (bevacizumab). Updated initial approval duration from 3 months to 6 months.	10/2022
Added new indication of stomach and esophagogastric adenocarcinoma based on clinical trial data that demonstrated overall survival in the third line treatment setting.	03/2019
Policy originally created and effective	5/2015

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP210

Description

Triheptanoin (Dojolvi) is a medium-chain triglyceride oral solution that provides a source of calories and fatty acids to bypass the long-chain enzyme deficiencies.

Length of Authorization

- Initial: Four months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
triheptanoin (Dojolvi)	8.3kcal/mL oral solution	Fatty acid oxidation disorders (LC-FAOD)	Monthly quantity to allow for a maximum of 35% of prescribed daily caloric intake

Initial Evaluation

- I. Triheptanoin (Dojolvi) may be considered medically necessary when the following criteria are met:
 - A. Member is diagnosed with **molecularly confirmed LC-FAOD** by a specialist in genetic metabolic disorders; **AND**
 - B. Member does not have pancreatic insufficiency; **AND**
 - C. Member has a history of hypoglycemia or cardiomyopathy or at least one episode of rhabdomyolysis; **AND**
 - D. Member has at least TWO of the following diagnostic criteria:
 1. One or more known gene mutations in: CPT2, ACADVL, HADHA, or HADHB; **OR**
 2. Disease specific elevation of acylcarnitines on a newborn blood spot or in plasma; **OR**
 3. Low enzyme activity in cultured fibroblasts; **AND**
 - E. Documentation of prescribed daily caloric intake is provided; **AND**
 - F. Provider attests that the member is utilizing dietary management (e.g. low fat, high carbohydrate diet, avoidance of fasting); **AND**
 - G. Provider attests that treatment with over the counter MCT oil has been ineffective, contraindicated, or not tolerated.
- II. Triheptanoin (Dojolvi) is considered investigational when used for all other conditions, including but not limited to:
 - A. Pancreatic insufficiency

- B. Fat malabsorption
- C. Impaired chylomicron transport
- D. Severe hyperchylomicronemia

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Prescriber attestation that the member has exhibited stability or improvement in disease activity [e.g., exercise tolerance, increased cardiac function tests]

Supporting Evidence

- I. Per National Organization for Rare Disorders (NORD), disease state management of LC-FAOD is directed toward preventing and controlling acute episodes, which include symptoms such as hypoglycemia, rhabdomyolysis, and cardiac complications. Management often involves avoidance of fasting, maintaining low-fat, high-carbohydrate diet, and using low-fat nutritional supplements and MCT oil available over the counter (OTC).
- II. Clinical presentation and the age of onset of LC-FAOD is variable. Signs and symptoms can be present at birth or develop later in adulthood. Even with treatment, many patients continue to experience symptom recurrence of variable frequency and severity. Hypoglycemia and cardiomyopathy typically occur at an earlier stage in life, rhabdomyolysis is usually present in asymptomatic patients later in adulthood. In addition to these three primary clinical manifestations, other symptoms are possible and include encephalopathy, peripheral neuropathy, and pigmentary retinopathy.
- III. The effectiveness of triheptanoin (Dojolvi) has been established based on one phase 2, randomized, double-blind trial comparing triheptanoin (Dojolvi) with trioctanoin in 32 adult and pediatric patients (aged 7 years and older). Patients had a confirmed diagnosis of LC-FAOD, evidence of at least one significant episode of rhabdomyolysis, and at least two of the following diagnostic criteria: disease specific elevation of acylcarnitines on a newborn blood spot or in plasma, low enzyme activity in cultured fibroblasts, or one or more known pathogenic mutations in CPT2, ACADVL, HADHA, HADHB.
- IV. The primary efficacy outcomes included changes in total energy expenditure (TEE), cardiac function by echocardiogram, exercise tolerance, and phosphocreatine recovery following acute exercise. Statistically significant outcomes were positive changes in left ventricular function and maximal heart rate reduction during an exercise tolerance test in the triheptanoin (Dojolvi) arm versus the trioctanoate arm.
- V. The quality of the evidence was considered low because the study had a small sample size and had incomplete blinding. Moreover, there were applicability issues as some primary endpoints (cardiac function and exercise tolerance) were not clinically significant.
- VI. Triheptanoin (Dojolvi) has not been directly compared to OTC MCT oil; therefore, there is insufficient evidence to conclude that triheptanoin (Dojolvi) is safer or more effective than OTC MCT oil.

- VII. The most commonly reported adverse reactions for triheptanoin (Dojolvi) include gastrointestinal upset, musculoskeletal pain, fatigue, and headache.
- VIII. There are no specific contraindications to using triheptanoin (Dojolvi), however, warnings include not using triheptanoin (Dojolvi) with feeding tubes manufactured of polyvinyl chloride (PVC) and avoiding use in patients with pancreatic insufficiency.
- IX. There is a lack of strong scientific evidence from randomized controlled trials supporting safety and efficacy for using triheptanoin (Dojolvi) for indications other than LC-FAOD.

Investigational or Not Medically Necessary Uses

- I. Triheptanoin (Dojolvi) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Pancreatic insufficiency
 - B. Fat malabsorption
 - C. Impaired chylomicron transport
 - D. Severe hyperchylomicronemia

Appendix

The recommended target daily dosage of triheptanoin (Dojolvi) is up to 35% of the patient's total prescribed daily caloric intake (DCI) divided into at least four doses and administered with mealtimes or with snacks.

- I. Table 1: Dosage initiation and titration

For patients not currently taking MCT product	- Initiate at total daily dosage of 10% DCI divided into four times per day. - Increase recommended daily dose of up to 35% DCI over a period of two to three weeks.
For patients switching from another MCT product	- Discontinue use of MCT products before starting triheptanoin (Dojolvi). - Initiate triheptanoin (Dojolvi) at the last tolerated daily dose of MCT divided into four times per day. - Increase the total daily dose by approximately 5% DCI every two to three days until target dose of up to 35% DCI is achieved.

- II. The quantity limit is to be determined based on the member's prescribed daily caloric intake (DCI). Maximum total daily dose may not exceed 35% DCI. Round the total daily dosage to the nearest whole number.

$$\text{Total Daily Dose (mL)} = \frac{\text{Member's DCI (kcal)} \times \text{Target (\% dose of DCI)}}{8.3 \text{ kcal/ml}}$$

References

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Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	11/2020

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP281

Description

Trofinetide (Daybue) is an insulin-like growth factor-1 (IGF-1) analogue, FDA-approved for the treatment of Rett syndrome (RTT) in adults and children 2 years of age and older. Trofinetide (Daybue) is administered orally or via a gastrostomy tube twice daily according to weight-based dosing.

Length of Authorization

- Initial: three months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
trofinetide (Daybue)	Rett syndrome (RTT)	200 mg/mL solution	Weight based (see appendix table)

Initial Evaluation

- I. **Trofinetide (Daybue)** may be considered medically necessary when the following criteria are met:
 - A. Member is 2 years of age or older; **AND**
 - B. Medication is prescribed by, or in consultation with a provider experienced in the diagnosis and management of Rett syndrome (e.g., pediatrician, neurologist, geneticist); **AND**
 - C. Documentation of member's weight within the last 3 months; **AND**
 - D. Member has a diagnosis of **classic or typical Rett syndrome**; **AND**
 1. Diagnosis is confirmed by genetic testing that documents a mutation in *MECP2* gene; **AND**
 2. Provider attestation diagnosis is confirmed by ALL of the following clinical features of classic or typical RTT:
 - i. Absence of grossly abnormal psychomotor development in first 6 months of life; **AND**
 - ii. A period of regression followed by recovery or stabilization; **AND**
 - iii. Partial or complete loss of acquired purposeful hand skills; **AND**
 - iv. Partial or complete loss of acquired spoken language; **AND**
 - v. Gait abnormalities: Impaired (dyspraxic) or absence of ability; **AND**
 - vi. Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing and washing/rubbing automatisms; **AND**
 - vii. Absence of brain injury secondary to trauma (peri- or postnatally), neurometabolic disease, or severe infection that causes neurological problems
- II. Trofinetide (Daybue) is considered investigational when used for all other conditions, including but not limited to:

- A. Pediatric patients less than 2 years of age
- B. Atypical or variant Rett syndrome (e.g., preserved speech (Zappella) variant, early onset seizures (Hanefeld) variant, and congenital (Rolando) variant)
- C. *MECP2*-mutation related disorders without clinical diagnostic symptoms of classic/typical Rett syndrome (e.g., *MECP2*-related severe neonatal encephalopathy, *PPMX*-syndrome, *MECP2* duplication syndrome)
- D. Other neurogenerative disorders or disorders that may have symptoms or physical features that are similar to Rett syndrome (e.g., autism spectrum disorder, encephalitis, spastic ataxia, cerebral palsy, spinocerebellar degeneration, leukodystrophies, neuroaxonal dystrophy)
- E. *CDKL5*-mutation disorders (e.g., infantile spasms, West syndrome, Lennox-Gastaut syndrome)
- F. Other metabolic or degenerative disorders (e.g., neuronal ceroid lipofuscinosis, phenylketonuria, and urea cycle disorders)
- G. *FOXP1*-mutation related disorders
- H. Pitt-Hopkins syndrome
- I. Angelman syndrome

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Documentation of member's weight within the last 3 months; **AND**
- IV. Provider attestation that trofinetide (Daybue) continues to slow or stabilize the progression of disease and treatment provides clinical benefit to the member.

Supporting Evidence

- I. Rett syndrome (RTT) is a progressive X-linked neurodevelopmental disorder that almost exclusively affects females. In the United States, approximately 11,000 patients are affected by RTT. Infants with RTT generally develop normally for about 6 to 18 months after birth, at which point regression of early milestones occurs. The ability to communicate, walk, and eat halt and begin to regress. Gradual deterioration continues into and throughout adulthood. Patients with RTT have a reduced life expectancy into the forties or fifties.
- II. Common features associated with progression of the disorder include severe loss of language skills, fine and gross motor skills, dysphagia, seizures, breathing abnormalities, growth failure, bone mineral deficits (including fractures), autonomic nervous system dysfunction, cardiac abnormalities, and tone abnormalities (dystonia and tremor).
- III. Diagnostic criteria for RTT is based on specific clinical criteria to reflect the main disease features. The clinical presentation associated with typical RTT is defined by a regression of purposeful hand use and spoken language, with the development of gait abnormalities and

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hand stereotypies. After the period of regression, a stage of stabilization and possibly improvement ensues, with some individuals partially regaining skills. Patients with atypical or variant RTT present with many of the clinical features of typical RTT, such as regression, but do not necessarily have all of the clinical features of typical RTT. There are three known forms of atypical RTT, including but not limited to the preserved speech (Zappella) variant, early onset seizures (Hanefeld) variant, and congenital (Rolando) variant RTT. Additional information about the diagnostic criteria are included in the appendix.

- IV. Approximately 90-95% of RTT cases are caused by identifiable mutations of the *MECP2* gene. In 99% of cases, these mutations occur sporadically and are not possessed or transmitted by a child's parents (de novo mutations). Therefore, the vast majority of cases of RTT are not an inherited disorder. Mutations in *MECP2* have also been identified in individuals who do not have the clinical features of RTT, usually a history of regression, and therefore cannot be given a diagnosis of RTT. These clinical phenotypes emphasize that mutations in *MECP2* are not synonymous with RTT and that a mutation in *MECP2* is not sufficient to make the diagnosis of RTT. The diagnosis of RTT is made clinically as *MECP2* mutations are neither necessary nor sufficient to make the diagnosis of RTT.
- V. Trofinetide (Daybue) is the first and only treatment FDA-approved to treat RTT. Treatments focus on managing symptoms and preventing complications. In addition to medications to help control specific symptoms, several non-drug approaches may be used to help manage the condition and improve patients' quality of life. All the treatments currently used are solely for management of the numerous complications of the disorder. These treatments include medications for epilepsy, constipation, and other systemic features, therapies to compensate for neurological impairment, and surgical therapies for dysphagia, contracture, and scoliosis are common. Functional abilities can be improved by various interventions such as physiotherapy, occupational therapy, hydrotherapy, and speech therapy. Given the complexity of the disease, diagnosis by a specialist or provider has consulted with a specialist in the area of the patient's diagnosis, such as a neurologist, pediatrician, or geneticist, is required.
- VI. Trofinetide (Daybue) is a synthetic version of a naturally occurring molecule known as glycine-proline-glutamate (GPE), the N-terminal tripeptide of insulin-like growth factor. The mechanism by which trofinetide (Daybue) exerts therapeutic effects in patients with Rett Syndrome (RTT) is unknown. In animal studies, trofinetide has been shown to increase branching of dendrites and synaptic plasticity signals.
- VII. The efficacy and safety of trofinetide (Daybue) were evaluated in the Phase 3 LAVENDER study, a 12-week, double-blind, randomized, placebo-controlled study that enrolled 187 female participants 5–20 years of age with RTT. Participants had a diagnosis of typical Rett syndrome according to the Rett Syndrome Diagnostic Criteria with a documented disease-causing mutation in the *MECP2* gene. Participants were randomized to receive trofinetide or matching placebo for 12 weeks. The trofinetide dosage was based on patient weight to achieve similar exposure in all patients. The co-primary endpoints included the Rett Syndrome Behavior Questionnaire (RSBQ) and Clinical Global Impression–Improvement (CGI-I) assessment.
 - a. The RSBQ is a 45-item rating scale completed by the caregiver that assesses core symptoms of Rett syndrome (breathing, hand movements or stereotypies, repetitive behaviors, night time behaviors, vocalizations, facial expressions, eye gaze, and mood). Each item is scored as 0 (not true), 1 (somewhat or sometimes true), or 2 (very true or

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often true), with a maximum possible score of 90 points. Lower scores reflect lesser severity in signs and symptoms of RTT.

- i. The mean baseline RSBQ score was 43.7 for the DAYBUE group and 44.5 for the placebo group.
 - b. The CGI-I is rated by clinicians to assess whether a patient has improved or worsened on a 7-point scale (1=very much improved to 7=very much worse) in which a lower score indicates improvement.
 - i. Baseline CGI-I score was 4.9 in both groups.
- VIII. Trofinetide (Daybue) demonstrated a statistically significant improvement over placebo in both co-primary endpoints. The RSBQ score change in trofinetide (Daybue) group was -4.9 compared to -1.7 change in placebo group was at week 12 (-3.2; 95% CI (-5.7, -0.6), $p=0.018$). The CGI-I score was 3.5 in the treatment group compared to 3.8 in the placebo group at week 12 (-0.3; 95% CI (-0.5- -0.1); $p=0.003$). A post-hoc analysis of CGI-I scores was conducted, which revealed that 61% of patients in the trofinetide (Daybue) had no change in RTT symptoms, while 25% had minimal improvement and 13% were much improved. In the placebo group, 81 % of patients had no change, 11% were minimally improved, and 5% were much improved.
- IX. The common adverse events were diarrhea (81% with trofinetide vs 19% with placebo) and vomiting (27% with trofinetide vs 10% with placebo). About 12% of trofinetide-treated subjects compared to 4% of placebo-treated subjects experienced weight loss of greater than 7% of body weight. Although a majority (>95%) of adverse events were rated as mild to moderate, the label warnings and precautions include diarrhea and weight loss to ensure prescribers and patients are aware of these adverse reactions. Treatment was discontinued in 17% individuals in the trofinetide group compared to 2% in the placebo group due to treatment related adverse events, with diarrhea (15%) as the most common adverse reaction leading to discontinuation. Due to the frequency of diarrhea, concomitant therapy with loperamide was initiated in over 50% of subjects in the LAVENDER trial.
- X. Although the LAVENDER trial enrolled patients age 5-20 years of age, trofinetide (Daybue) is FDA approved for the treatment of RTT in adults and pediatric patients 2 years of age and older. Efficacy in pediatric patients with RTT aged 2 to 4 years old was provided by an open-label PK study in which 13 patients completed 12 weeks of treatment with trofinetide (Daybue). Exposure and adverse reactions in pediatric patients 2 to 4 years of age treated with trofinetide (Daybue) were similar to those reported in adult and pediatric patients 5 years of age and older in the LAVENDER study.
- XI. The inclusion criteria in the LAVENDER study enrolled all female participants, required all participants to have a diagnosis of classic or typical RTT (per diagnostic criteria from Neul et al. 2010), and confirmed *MECP2* mutation. The study excluded patients with atypical RTT, patients without a documented *MECP2* mutation, and male subjects to reduce variability and allow for a more homogeneous study population. Coverage of trofinetide (Daybue) will be considered for individuals with a confirmed clinical diagnosis of typical RTT and presence of *MECP2* mutation to mirror the study population. As of July 2023, efficacy and safety of trofinetide (Daybue) in patients with atypical RTT is unknown.
- XII. The available evidence demonstrates statistically significant improvements in the primary endpoints studied, RSBQ and CGI-I, when trofinetide (Daybue) was compared to placebo. There is low to moderate confidence that trofinetide (Daybue) provides clinically meaningful symptom

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relief or affects physical functioning due to lack of established minimal clinically important differences in the RSBQ and CGI-I scoring instruments. Additionally, the scoring instruments used as primary outcomes are subjective in nature and introduce assessment bias concerns. The impact of trofinetide (Daybue) on morbidity, mortality, or health-related quality of life among patients with RTT is also unknown. The impact of trofinetide (Daybue) on disease activity over time is unknown, however long-term data is currently being assessed in two Phase 3 open-label extension trials (LILAC-1, LILAC-2).

Investigational or Not Medically Necessary Uses

- I. Trofinetide (Daybue) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Pediatric patients less than 2 years of age
 - B. Atypical or variant Rett syndrome (e.g., preserved speech (Zappella) variant, early onset seizures (Hanefeld) variant, and congenital (Rolando) variant)
 - C. *MECP2*-mutation related disorders without clinical diagnostic symptoms of classic/typical Rett syndrome (e.g., *MECP2*-related severe neonatal encephalopathy, *PPMX*-syndrome, *MECP2* duplication syndrome)
 - D. Other neurogenerative disorders or disorders that may have symptoms or physical features that are similar to Rett syndrome (e.g., autism spectrum disorder, encephalitis, spastic ataxia, cerebral palsy, spinocerebellar degeneration, leukodystrophies, neuroaxonal dystrophy)
 - E. *CDKL5*-mutation disorders (e.g., infantile spasms, West syndrome, Lennox-Gastaut syndrome)
 - F. Other metabolic or degenerative disorders (e.g., neuronal ceroid lipofuscinosis, phenylketonuria, and urea cycle disorders)
 - G. *FOXP1*-mutation related disorders
 - H. Pitt-Hopkins syndrome
 - I. Angelman syndrome

Appendix

- I. Table 1: Quantity Limit/Dosing
 - A. Available dosage form: Trofinetide 200mg/mL oral solution is available as a 450mL strawberry flavored oral solution in 500mL bottle
 - B. Per the label, any unused trofinetide (Daybue) should be discarded after 14 days of first opening the bottle
 - C. The dose prescribed is appropriate based on the individual's weight:

Patient Weight	Trofinetide (Daybue) Dosing	Trofinetide (Daybue) Volume	mL/Day supply (DS)	# Bottles/Day supply (DS)
9kg to less than 12kg	5,000 mg twice daily	25mL twice daily	1,500mL/27 days	3 bottles/27 days
12kg to less than 20kg	6,000 mg twice daily	30mL twice daily	2,000mL/30 days	4 bottles/30 days
20kg to less than 35kg	8,000 mg twice daily	40mL twice daily	2,500mL/28 days	5 bottles/28 days
35kg to less than 50kg	10,000 mg twice daily	50mL twice daily	3,000mL/28 days	6 bottles/28 days
50kg or more	12,000 mg twice daily	60mL twice daily	4,000mL/30 days	8 bottles/30 days

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II. Table 2. Rett Syndrome Diagnostic Criteria (Source: Neul et al. 2010)

Required for typical or classic RTT
1. A period of regression followed by recovery or stabilization[*] 2. All main criteria and all exclusion criteria 3. Supportive criteria are not required, although often present in typical RTT
Main Criteria
1. Partial or complete loss of acquired purposeful hand skills. 2. Partial or complete loss of acquired spoken language^{**} 3. Gait abnormalities: Impaired (dyspraxic) or absence of ability. 4. Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing and washing/rubbing automatisms
Exclusion Criteria for typical RTT
1. Brain injury secondary to trauma (peri- or postnatally), neurometabolic disease, or severe infection that causes neurological problems^{***} 2. Grossly abnormal psychomotor development in first 6 months of life[#]
Required for atypical or variant RTT
1. A period of regression followed by recovery or stabilization[*] 2. At least 2 out of the 4 main criteria 3. 5 out of 11 supportive criteria
Supportive Criteria for atypical RTT^{##}
1. Breathing disturbances when awake 2. Bruxism when awake 3. Impaired sleep pattern 4. Abnormal muscle tone 5. Peripheral vasomotor disturbances 6. Scoliosis/kyphosis 7. Growth retardation 8. Small cold hands and feet 9. Inappropriate laughing/screaming spells 10. Diminished response to pain 11. Intense eye communication - "eye pointing"
[*]Because <i>MECP2</i> mutations are now identified in some individuals prior to any clear evidence of regression, the diagnosis of "possible" RTT should be given to those individuals under 3 years old who have not lost any skills but otherwise have clinical features suggestive of RTT. These individuals should be reassessed every 6–12 months for evidence of regression. If regression manifests, the diagnosis should then be changed to definite RTT. However, if the child does not show any evidence of regression by 5 years, the diagnosis of RTT should be questioned. ^{**}Loss of acquired language is based on best acquired spoken language skill, not strictly on the acquisition of distinct words or higher language skills. Thus, an individual who had learned to babble but then loses this ability is considered to have a loss of acquired language. ^{***}There should be clear evidence (neurological or ophthalmological examination and MRI/CT) that the presumed insult directly resulted in neurological dysfunction. [#]Grossly abnormal to the point that normal milestones (acquiring head control, swallowing, developing social smile) are not met. Mild generalized hypotonia or other previously reported subtle developmental alterations during the first six months of life is common in RTT and do not constitute an exclusionary criterion. ^{##}If an individual has or ever had a clinical feature listed it is counted as a supportive criterion. Many of these features have an age dependency, manifesting and becoming more predominant at certain ages. Therefore, the diagnosis of atypical RTT may be easier for older individuals than for younger. In the case of a younger individual (under 5 years old) who has a period of regression and ≥2 main criteria but does not fulfill the requirement of 5/11 supportive criteria, the diagnosis of "probably atypical RTT" may be given. Individuals who fall into this category should be reassessed as they age and the diagnosis revised accordingly.

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Related Policies

Currently there are no related policies.

Policy Implementation/Update

Action and Summary of Changes	Date
Policy created	08/2023

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP194

Split Fill Management*

Description

Tucatinib (Tukysa) is an orally administered tyrosine kinase inhibitor that targets the growth of HER2-expressing tumors.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
tucatinib (Tukysa)	HER2- positive metastatic breast cancer	50 mg tablets	60 tablets/30 days
	HER2-positive RAS wild-type unresectable or metastatic colorectal cancer	150 mg tablets	120 tablets/30 days

Initial Evaluation

- I. **Tucatinib (Tukysa)** may be considered medically necessary when the following criteria are met:
 - A. Member is 18 years of age or older; **AND**
 - B. Medication is prescribed by, or in consultation with, an oncologist; **AND**
 - C. The member has **not** previously progressed on or after treatment with another tyrosine kinase inhibitor (e.g., lapatinib [Tykerb], neratinib [Nerlynx]); **AND**
 - D. A diagnosis of **advanced or metastatic breast cancer** when the following are met:
 1. Documentation is provided showing the disease is HER2-positive; **AND**
 2. Will be used in combination with trastuzumab and capecitabine; **AND**
 3. Will not be used with any other oncology therapy outside of trastuzumab and capecitabine; **AND**
 4. Member does **not** have brain metastases; **AND**
 - i. Member has progressed on, has a contraindication to, or did not tolerate treatment with trastuzumab, pertuzumab, and trastuzumab emtansine (TDM-1); **OR**
 5. Member has brain metastases; **AND**
 - i. Member has received ≥1 prior anti-HER2-based regimens in the metastatic setting

- I. Tucatinib (Tukysa) is considered investigational when used for all other conditions, including but not limited to:
 - A. Metastatic colorectal cancer

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Member has experienced response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread; **AND**
- IV. Tucatinib (Tukysa) will be used in combination with trastuzumab and capecitabine; **AND**
- V. Tucatinib (Tukysa) will not be used with any other oncology therapy outside of trastuzumab and capecitabine

Supporting Evidence

- I. Tucatinib (Tukysa) was studied in a phase 2, double blind, placebo controlled, randomized trial (HER2CLIMB) in 612 patients with HER2-positive metastatic breast cancer with, or without, brain metastases who had been previously treated with trastuzumab, pertuzumab, and trastuzumab emtansine (TDM-1). The trial evaluated treatment with tucatinib (Tukysa) in combination with trastuzumab and capecitabine versus placebo, trastuzumab, and capecitabine. Patients in the trial had a median of 4 previous lines of therapy and 48% of patients had brain metastases. Overall survival at 2 years was 44.9% with the tucatinib (Tukysa) combination and 26.6% with trastuzumab, capecitabine, and placebo combination (hazard ratio for death, 0.66; 95% CI, 0.50-0.88; P = 0.005). Median overall survival was 21.9 months (tucatinib (Tukysa) combination) and 17.4 months (placebo, trastuzumab, and capecitabine). Secondary outcome of progression free survival at 1 year in patients with brain metastases was 24.9% with the tucatinib (Tukysa) combination and 0% with trastuzumab, capecitabine, and placebo combination (hazard ratio, 0.48; 95% CI, 0.34-0.69; P < 0.001).
- II. Patients in the HER2CLIMB trial were excluded if they were previously treated with neratinib, afatinib, or any HER2 tyrosine kinase inhibitor at any time previously. Those who were treated with lapatinib more than 12 months from the start of the study were allowed to enroll in the trial; however, this accounted for only 6% of patients in the HER2CLIMB trial. At this time, there is lack of scientific evaluation for safety and efficacy of tucatinib (Tukysa) following progression on or after another tyrosine kinase inhibitor.
- III. Although patients in the trial were heavily pretreated having failed trastuzumab, pertuzumab, and trastuzumab emtansine (TDM-1), FDA approval was granted in adults with or without brain metastases who have received ≥1 prior anti-HER2-based regimens in the metastatic setting. Agents such as TDM-1 and other oral tyrosine kinase inhibitors (i.e., neratinib, lapatinib) also have FDA approval and overall survival data in the previously treated metastatic setting. No

head to head trials are available comparing tucatinib (Tukysa) to other tyrosine kinase inhibitors in this space.

- IV. Given the population included in the HER2CLIMB trial consisted of heavily pretreated patients, criteria for coverage is set to reflect this patient population. Patients with CNS metastases, however, require only ≥ 1 prior anti-HER2-based regimen given limited treatment options and lack of strong data with other therapies in this population.

Investigational or Not Medically Necessary Uses

- I. Tucatinib (Tukysa) has not been sufficiently studied for safety or efficacy for the following indication(s):
- A. Metastatic colorectal cancer, RAS wild-type, HER2+
- i. HER2 is overexpressed in 3-5% of patients with mCRC and in 10% of patients with RAS wild type mCRC. Tucatinib (Tukysa) with trastuzumab is the first FDA-approved treatment, under accelerated approval, for HER2-positive RAS wild-type unresectable or metastatic colorectal cancer (mCRC) with progression following treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy.
 - ii. Tucatinib was studied in a phase II, open-label, cross over multicenter trial. The trial was initially designed as a single arm study with 45 participants enrolled to receive tucatinib 300mg orally twice daily with trastuzumab (loading dose of trastuzumab 8mg/kg IV on day 1 of cycle 1, maintenance dose of trastuzumab 6mg/kg on day 1 of each subsequent 21 day cycle). The trial was then expanded globally to include patients who were randomly assigned to receive tucatinib plus trastuzumab (cohort B, N=41) or tucatinib monotherapy (cohort C, N=31). Cohort C was allowed to cross over from tucatinib monotherapy to tucatinib + trastuzumab combination therapy was allowed after 12 weeks if there was disease progression at any time. All participants had to have HER2-positive, RAS wildtype, unresectable or metastatic CRC and received prior treatment with fluoropyrimidines, oxaliplatin, irinotecan, and anti-vascular endothelial growth factor (VEGF) monoclonal antibody, and anti-PD-1 therapy. Participants were not allowed to have received prior anti-HER2 targeting therapy. Participants were treated until disease progression or unacceptable toxicity. The median age was 55 years, 14% of participants were >65 years, 67% white, 61% male, 70.2% of participants had lung metastases, 64.3% had lung metastases. Ninety-nine percent of participants received prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan, 83% and 52% received anti-VEGF antibodies and anti-EGFR antibodies.
 - iii. The primary outcome was overall response rate (ORR) with secondary endpoints of duration of response, progression-free survival, overall survival and adverse events. After a median follow-up of 20.7 months, efficacy was evaluated in 84 patients. Cohort A and B had a confirmed ORR per blinded independent central review (BICR) of 38.1%, median duration of response 12.4 months, median PFS of 8.2 months (95% CI, 4.2-10.3), and a median OS of 24.1 months (95% CI, 20.3-36.7). Results for the secondary end points showed a median PFS of 8.2 months

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(95% CI, 4.2-10.3), and a median OS of 24.1 months (95% CI, 20.3-36.7), in the combination cohorts.

- iv. The most common grade ≥ 3 toxicity was hypertension (7%), ALT elevation (3%), AST elevation (2%), hypertransaminasemia (1%). There were no deaths related to toxicity.
- v. As of March 2023, current subsequent therapy recommendations for HER2-amplified RAS wild-type mCRC after progression following treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy are based on limited evidence. NCCN guidelines currently recommend trastuzumab with tucatinib (or pertuzumab (Perjeta) or lapatinib (Tykerb)) if the patient has not had prior HER2 treatment (category 2A recommendation). NCCN guideline directed therapies, trastuzumab with pertuzumab (Perjeta) or lapatinib (Tykerb), for HER2-positive RAS wild-type mCRC are not FDA approved and considered off-label use. After progression following treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, NCCN guidelines recommend trifluridine and tipiracil (Lonsurf) and regorafenib (Stivarga) for mCRC irrespective of HER2 and KRAS mutations and encorafenib (Braftovi) for mCRC in combination with cetuximab (Erbix) for mCRC with BRAF V600E mutation. Trifluridine and tipiracil (Lonsurf), regorafenib (Stivarga), and encorafenib (Braftovi) are FDA approved for treatment of mCRC.
- vi. There is unknown clinical impact on the overall survival rate, health quality of life, or symptom improvement in participants treated with tucatinib and trastuzumab. Results from this phase II trial may be subjected to confounders and biases due to lack of a comparator and an open-label design. ORR is a surrogate marker and does not directly measure clinical outcomes. Change in ORR does not predict morbidity or mortality outcomes. Confirmatory trials are needed to establish safety and efficacy of tucatinib in mCRC, and therefore coverage for tucatinib (Tukysa) for mCRC is considered experimental and investigational.
- vii. Despite the accelerated FDA-approval, continued approval of tucatinib (Tukysa) as a subsequent-line treatment of MCL, remains contingent upon verification of clinical benefit in confirmatory trials. There is an ongoing trial to evaluate tucatinib (Tukysa) in HER2-positive mCRC in the ongoing global, randomized Phase 3 clinical trial (MOUNTAINEER-03), comparing tucatinib (Tukysa) in combination with trastuzumab and mFOLFOX6 with standard of care. This trial is intended to serve as the confirmatory trial that is required as part of the accelerated approval pathway.

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
lapatinib (Tykerb)	Breast cancer
neratinib (Nerlynx)	Breast cancer, early stage, HER2-positive, following trastuzumab Breast cancer, advanced or metastatic HER2-positive
gonadotropin-releasing hormone (GnRH)	Advanced breast cancer in premenopausal women
regorafenib (Stivarga)	Colorectal cancer, metastatic, previously treated
encorafenib (Braftovi), binimetinib (Mektovi)	Colorectal cancer, metastatic, BRAF V600E mutation, combination therapy
trifluridine/tipiracil (Lonsurf)	Colorectal cancer, metastatic, previously treated

Policy Implementation/Update

Action and Summary of Changes	Date
Policy updated to include MOUNTAINEER trial results in E/I section for metastatic colorectal cancer.	03/2023
Updated policy formatting. Added related policies. Updated supporting evidence, references.	
Policy created	08/2020

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP034

Description

Glycerol phenylbutyrate (Ravicti) and sodium phenylbutyrate (Buphenyl, Pheburane, Olpruva) are orally administered nitrogen-binding agents used in the treatment of urea cycle disorder (UCD).

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
sodium phenylbutyrate (generic Buphenyl)	Urea Cycle Disorder	500mg tablets	1200 tablets/30 days [∞]
		3g/tsp powder (250g bottle)	600 grams/30 days [∞]
sodium phenylbutyrate (Buphenyl)		500mg tablets	1200 tablets/30 days [∞]
		3g/tsp powder (250g bottle)	600 grams/30 days [∞]
sodium phenylbutyrate (Pheburane)		Oral pellets (84g bottle)	600 grams/30 days [∞]
glycerol phenylbutyrate (Ravicti)		1.1g/mL (25mL bottle)	525 mL (570g)/30 days*
sodium phenylbutyrate (Olpruva)		2 gm packets for suspension	90 packets/30 days
		3 gm packets for suspension	
		4 gm packets for suspension	
		5 gm packets for suspension	
	6 gm packets for suspension		
	6.67 gm packets for suspension		

*Glycerol phenylbutyrate (Ravicti) max dose of 17.5ml/day (no more than 19 g/day)

[∞]Sodium phenylbutyrate (Buphenyl, Pheburane) max dose of 20g/day

Initial Evaluation

- I. **Sodium phenylbutyrate (Buphenyl, Pheburane, Olpruva)** may be considered medically necessary when the following criteria below are met:
 - A. Member is diagnosed with **Urea Cycle Disorder (UCD)** when the following are met:
 1. Management by dietary protein restriction and amino acid supplementation alone has been ineffective; **AND**

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2. Member will continue dietary protein restriction and, if needed, amino acid supplementation; **AND**
 3. Documentation of baseline ammonia level indicating member has hyperammonemia (ammonia level is above the upper limit of normal based on member's age); **OR**
 - i. Member is transitioning from IV amino acid infusion (sodium phenylacetate/sodium benzoate) to oral therapy; **AND**
 - B. Treatment with generic sodium phenylbutyrate has been ineffective, contraindicated, or not tolerated; **AND**
 - C. Member must demonstrate a medical reason they are unable to utilize generic sodium phenylbutyrate. Convenience of administration route or palatability preference does not equate to medical necessity (documentation required); **AND**
 1. For brand sodium phenylbutyrate (Buphenyl) tablets:
 - i. Member weighs at least 20 kg (44 lbs.)
- II. **Glycerol phenylbutyrate (Ravicti)** may be considered medically necessary when the following criteria below are met:
- A. Member meets criteria IA-IB; **AND**
 - B. Member must demonstrate a medical reason they are unable to utilize sodium phenylbutyrate products (Buphenyl, Pheburane, Olpruva). Convenience of administration route or palatability preference does not equate to medical necessity (documentation required).
- III. Glycerol phenylbutyrate (Ravicti), sodium phenylbutyrate (Buphenyl, Pheburane, Olpruva) are considered investigational when used for all other conditions, including but not limited to:
- A. Amyotrophic lateral sclerosis (ALS)
 - B. Acute hyperammonemia
 - C. N-acetylglutamate synthase (NAGS) deficiency

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Provider attestation member will be continuing dietary protein restriction and, if needed, amino acid supplementation; **AND**
- IV. Member has exhibited a reduction from baseline in plasma ammonia levels; **OR**
 - A. Member has maintained a plasma ammonia level within normal range for member's age (see supporting evidence for normal ranges)

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Supporting Evidence

- I. Urea cycle disorders (UCD) are rare genetic metabolic deficiencies caused by missing enzymes in the urea cycle, the most common being ornithine transcarbamylase (OTC) deficiency. All of the following are known UCDs: carbamylphosphate synthetase I [CPS1], ornithine transcarbamylase [OTC], argininosuccinic acid synthetase [ASS1], argininosuccinic acid lyase [ASL], arginase [ARG], and N-acetyl glutamate synthetase [NAGS]. In UCD, the body is unable to convert the excess amino acids from food breakdown into uric acid that is secreted from the body resulting in high levels of ammonia in the body. In most cases, onset of symptoms occurs at, or shortly following, birth (neonatal period); however, some individuals may not exhibit hyperammonemia or symptoms until later during infancy, childhood, or even adulthood due to a partial enzyme deficiency. It is important that the diagnosis and treatment be started early to improve survival.
- II. An elevated plasma ammonia level of 150 $\mu\text{mol/L}$ ($>260 \mu\text{g/dl}$), or higher, in neonates and $> 100 \mu\text{mol/L}$ ($175 \mu\text{g/dl}$) in older children and adults, is a strong indication for the presence of a urea cycle disorder. Hyperammonemia can be the first symptom in patients without a known family history of UCD or without knowing the patient's genetics. Normalization of ammonia levels is critical to prevent neurologic abnormalities and impaired cognitive function in hyperammonemia. Acute management includes hemodialysis, fluid management, and IV infusion of sodium phenylacetate-sodium benzoate. Once patients are stabilized (ammonia level $<100 \text{ mmol/L}$ and mental status returns to baseline), patients can transition to oral therapy (sodium phenylbutyrate or glycerol phenylbutyrate). Per Orphanet Guidelines for Rare Diseases, not all patients who recover from an episode of hyperammonemia require chronic nitrogen-scavenging agents, but they should be considered if the patient cannot manage the disease with dietary treatment alone.
- III. The goal of long-term management of UCD are to prevent hyperammonemia and includes dietary restrictions of protein, use of specialized formulas (in infants and young children), and oral nitrogen-scavenging agents. Sodium phenylbutyrate (Buphenyl, Pheburane, Olpruva) and glycerol phenylbutyrate (Ravicti) and are nitrogen-binding agents used in the chronic management of patients with UCD involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (AS), that cannot be managed by dietary protein restriction and/or dietary supplementation alone. Treatment must be combined with dietary protein restriction and, in some cases, dietary/amino acid supplementation (e.g., essential amino acids, arginine, citrulline, protein-free calorie supplements). Poor adherence with prescribed diets may increase the patient's protein intake, which may necessitate a dosage increase; therefore, attestation of continuing dietary protein restriction and/or, amino acid supplementation is required.
- IV. Sodium phenylbutyrate (Buphenyl, Pheburane, Olpruva) has more real-world data due to the time on the market as sodium phenylbutyrate was approved in 1996 and glycerol phenylbutyrate (Ravicti) was not approved until 2013. Sodium phenylbutyrate (Pheburane) was approved via 505(b)(2) pathway in 2022 and shares the same indication as Buphenyl. There have been several head-to-head non-inferiority studies in both adults and pediatrics, that showed glycerol phenylbutyrate (Ravicti) is as effective as sodium phenylbutyrate (Buphenyl, Pheburane, Olpruva) in treating UCD and has a slightly improved tolerability overall (no salty taste and odorless). Although, there is more data in the use of sodium phenylbutyrate (Buphenyl, Pheburane, Olpruva) and because it is specifically indicated in ornithine transcarbamylase (OTC)

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therapy, the most common UCD; sodium phenylbutyrate (Buphenyl, Pheburane, Olpruva) is typically started if UCD is suspected, and a genetic profile has not yet been completed. Additionally, in the absence of a clinically significant difference in efficacy between glycerol phenylbutyrate (Ravicti) and sodium phenylbutyrate (Buphenyl, Pheburane, Olpruva), generic sodium phenylbutyrate is chosen as the preferred agent in the setting of UCD due to generic availability, cost, and a larger pool of safety and efficacy data.

- V. Documentation of medical necessity for glycerol phenylbutyrate (Ravicti) and sodium phenylbutyrate (Buphenyl, Pheburane, Olpruva) is required, as the recommended dose can be obtained with the generic sodium phenylbutyrate, providing a significant price differential (3 – 10x difference). Acceptable rationale for medical necessity include difficulty swallowing, restricted sodium intake, etc. Convenience of administration route or palatability preference does not equate to medical necessity.
- VI. The notable differences between glycerol phenylbutyrate (Ravicti) and sodium phenylbutyrate (Buphenyl) is the unpleasant smell/taste and the higher than the recommended daily allowance of sodium in sodium phenylbutyrate (Buphenyl, Pheburane, Olpruva). Sodium phenylbutyrate products should be used with caution in patients who have conditions that cause edema and/or must maintain restricted sodium intake (congestive heart failure, severe renal insufficiency, cirrhosis, or nephrosis). It is recommended that patients that develop new onset edema or worsening edema with sodium phenylbutyrate discontinue sodium phenylbutyrate products. Furthermore, generic sodium phenylbutyrate and brand sodium phenylbutyrate (Buphenyl) are both available in tablet and powder formulations and are known to have a distinct, strong salty taste. Glycerol phenylbutyrate (Ravicti) is available as a tasteless/odorless oral solution. Sodium phenylbutyrate (Pheburane) shares the same indication as generic sodium phenylbutyrate and Buphenyl, however is formulated as tasteless/odorless oral pellets. Generic sodium phenylbutyrate powder, Buphenyl powder, and glycerol phenylbutyrate (Ravicti) are able to be administered via nasogastric or gastrostomy tube.
- VII. Clinical study results showed ammonia values ranged from 9-35 µmol/L; however, the US UCD management guidelines do not specify a direct chronic ammonia treatment target number. Additionally, the normal value changes from neonates, to pediatrics, to adults and the consensus would be to focus on keeping the body within the normal range for the patient's age on the lab test used, see below table.

Ammonia Level Range Table	
Age Range	Normal Ammonia Range
Adults	7-35 mmol/L
Children	28-57 mmol/L
Newborns	64-107 mmol/L

- VIII. The quantity limits noted in the table above reflect the maximum daily dose for each agent as there have not been safety/efficacy data over these doses. If the patient is transitioning from sodium phenylbutyrate (Buphenyl, Pheburane, Olpruva) to glycerol phenylbutyrate (Ravicti), a slight initial dosage change to ensure the patient is receiving the same amount of phenylbutyric acid, is required. See appendix for details.

Investigational or Not Medically Necessary Uses

- I. Amyotrophic Lateral Sclerosis (ALS)

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- A. In a phase 2 clinical study (CENTAUR), 137 patients with ALS were randomized 2:1 to receive sodium phenylbutyrate combined with taurursodiol (PB-TURSO) [N=89] or placebo [N=48], for 6 months. The primary endpoint was the ability to slow the disease progression as measured by changes in the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R). The ALSFRS-R is the principal functional end point referenced in the latest FDA guidance for ALS trials with each point decrease representing lost capability across a 12 point scale, looking at tasks such as breathing, walking, fine motor skills; a higher score meaning higher normal function and less progressed disease symptoms. The primary endpoint was the only endpoint to reach statistical significance with a p-value of 0.03 and a mean rate of change in the ALSFRS-R scores of -1.24 points per month for PB-TURSO versus -1.66 points in placebo. With an absolute mean difference at week 24 of 2.32 in PB-TURSO versus placebo correlating to preserved functioning ability in those taking the study compound over placebo.
 - B. An open-label extension (OLE) was allowed for those who completed the CENTAUR trial (97 patients in total between both arms) for up to 30 months. Fifty-six patients on PB-TURSO and 34 on placebo enrolled, all receiving PB-TURSO in the OLE, those originally on placebo were changed over. The risk of key events including death, tracheostomy, first hospitalization and progression-free survival were all evaluated. Median key event-free survival duration was 4.8 months longer in participants originally randomized to PB-TURSO versus placebo, and median tracheostomy/PAV-free survival duration was 7.3 months longer. As of the analysis cut-off, median time to first hospitalization was not yet reached in the group originally randomized to PB-TURSO, compared with 14.1 months in the group originally randomized to placebo.
 - C. The OLE noted that this added to the previously reported overall functional/survival benefits from the primary phase 2 randomized, blinded trial. On September 7th, a second FDA advisory panel met to discuss the phase 2 and OLE data, as the March panel negatively reviewed this data pushing back the first PDUFA date by several months. On September 7th, the committee was 7-2 favorable, changing their prior decision. Currently, there is a recruiting phase 3 trial (PHOENIX) and a PDUFA date on September 29th. If approved, PB-TURSO would be an add-on agent to those already approved in the treatment of ALS, riluzole, and edaravone. At this time, sodium phenylbutyrate is considered experimental and investigational for the treatment of ALS.
- II. Acute hyperammonemia
 - A. Neither glycerol phenylbutyrate (Ravicti) nor sodium phenylbutyrate (Buphenyl, Pheburane, Olpruva) are indicated to treat acute hyperammonemia, which is considered a life-threatening emergency. Rapidly acting interventions are essential to reduce plasma ammonia levels. Treatment of acute hyperammonemia includes stopping protein intake, hydration, and initiation of IV arginine hydrochloride, sodium benzoate/sodium phenylacetate (Ammonul), and/or oral citrulline.
 - III. N-acetylglutamate synthase (NAGS) deficiency
 - A. The efficacy and safety of glycerol phenylbutyrate (Ravicti) for the treatment of hyperammonemia due N-acetylglutamate synthase (NAGS) deficiency has not been established.

Appendix

- I. The recommended dosages for patients that are treatment naïve or switching from sodium phenylbutyrate (Buphenyl, Pheburane, Olpruva) to phenylbutyrate (Ravicti) are different. A direct conversion of dosing can be calculated for patients already on sodium phenylbutyrate (Buphenyl, Pheburane, Olpruva) to sodium phenylbutyrate (Ravicti):
 - a. Total daily dose glycerol phenylbutyrate (mL) = 0.8 x total daily dose of sodium phenylbutyrate (grams)

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6. Lee B, Diaz GA, Rhead W, et al. Blood ammonia and glutamine as predictors of hyperammonemic crises in patients with urea cycle disorder. *Genetics in Medicine*. 2015;17(7):561-568.
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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
carbglu (carglumic acid)	Acute hyperammonemia due to NAGS deficiency
	Chronic hyperammonemia due to NAGS deficiency
	Acute hyperammonemia due to PA or MMA

Policy Implementation/Update

Action and Summary of Changes	Date
Added new product, sodium phenylbutyrate (Olpruva) to policy.	06/2023
Added new product, sodium phenylbutyrate (Pheburane) to policy. Added generic sodium phenylbutyrate to QL table. Expanded on quantity limits to meet weight-based dosing. Updated formatting to separate generic SPB, Buphenyl, Pheburane, and Ravicti. Removed age requirement. Removed ammonia lab requirement in initial criteria and replaced with documentation of baseline level, allow coverage in members transitioning from IV to oral therapy; added requirement of documentation of medical necessity for branded products; added attestation for continuing amino acid supplementation/diet in renewal, added NAGS to E/I and updated E/I evidence. Updated supporting evidence and references. Added appendix and related policies section.	09/2022

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Updated policy name, added second medication to the policy, sodium phenylbutyrate. Expanded on quantity limits to meet weight-based dosing; added clinical criteria for review of sodium phenylbutyrate. Updated renewal criteria. Added ALS as experimental indication. Revised and strengthened the supporting evidence.	12/2021
Criteria update: Included new FDA expanded indication for pediatric patients 2 months and older. Glycerol phenylbutyrate (Ravicti) was originally approved for pediatric patients 2 years and older. Additionally, a question was added to the renewal portion of this policy to assess for toxicity.	01/2019
Previous Reviews	07/2013; 08/2013

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP216

Description

Uridine triacetate (Xuriden) is a pyrimidine analog for uridine replacement indicated in adult and pediatric patients for the treatment of hereditary orotic aciduria (HOA).

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
uridine triacetate (Xuriden)	2 g/packet	Hereditary orotic aciduria	240 g/30 days

Initial Evaluation

- I. Uridine triacetate (Xuriden) may be considered medically necessary when the following criteria are met:
 - A. Member is diagnosed with **hereditary orotic aciduria (HOA)** by a provider specializing in the patient's diagnosis or in consultation with a geneticist, hematologist or specialist in metabolic disorders; **AND**
 - B. Member has at least ONE of the following diagnostic criteria:
 1. Molecular genetic test indicating variations in uridine monophosphate synthetase (UMPS) gene; **OR**
 2. Urine test indicating high levels of orotic acid and/or orotidine; **AND**
 - C. Member has severe disease as defined by one or more of the following:
 1. Hematologic abnormalities (e.g. megaloblastic anemia, neutropenia, leukopenia); **OR**
 2. Renal tract obstruction (due to aggregation of orotic acid crystals); **OR**
 3. Immune dysfunction; **OR**
 4. Congenital anomalies; **OR**
 5. Physical and intellectual developmental delays; **AND**
 - D. Provider attestation that member does not have ornithine transcarbamoylase (OTC) deficiency; **AND**
 1. Blood ammonia levels are within normal limits
- II. Uridine triacetate (Xuriden) is considered investigational when used for all other conditions, including but not limited to:
 - A. Fluoropyrimidine overdose/overexposure

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Prescriber attestation that the member has exhibited stability or improvement in disease symptoms [e.g., improvement in hematologic status, improvement in growth]

Supporting Evidence

- I. HOA is an extremely rare genetic disorder affecting both men and women, with fewer than 25 cases of patients with this disorder worldwide have been reported in the medical literature. It is caused by variations in the uridine monophosphate synthase (UMPS) gene which is responsible for producing an enzyme that catalyzes the last two steps of the pyrimidine biosynthesis pathway. One of these two final steps is to convert orotic acid into another chemical substance. Because of the variation in the UMPS gene, individuals with this disorder have low levels of the enzyme needed to breakdown orotic acid and subsequently have a reduced production of uridine, a nucleotide involved in multiple essential physiological functions including biosynthesis of RNA, synthesis of glycogen and glycoprotein, phospholipid synthesis, and DNA synthesis.
- II. The exact mechanism by which orotic acid buildup and uridine monophosphate synthase deficiency leads to signs and symptoms of the disease is not completely understood. Orotic acid is believed to improve the metabolism of folic acid and vitamin B12 and may play a role in gene transcription.
- III. HOA is a clinically heterogenous disorder and individuals who retain some UMPS activity may be asymptomatic or only mildly affected. Features of more severe disease include megaloblastic anemia that is not responsive to treatment with vitamin B12 or folic acid, neutropenia, renal tract obstruction (due to aggregation of orotic acid crystals), immune dysfunction, congenital anomalies, and physical and intellectual developmental delays.
- IV. Diagnosis of HOA is confirmed by assessment of symptoms, family history, a urine test indicating high levels of orotic acid and/or orotidine, and a molecular genetic test indicating variations in uridine monophosphate synthetase (UMPS) gene. Not all patients will present with elevated orotic acid and/or orotidine urine levels; however, this is the most common laboratory abnormality seen in 80%-99% of patients. Deferential diagnosis of HOA includes urea cycle disorders one of which may also present with high blood levels of orotic acid, this disorder is known as ornithine transcarbamoylase (OTC) deficiency. OTC can be distinguished from HOA by evaluation of blood ammonia levels. Patients with HOA will have normal blood ammonia levels, whereas, patients with OTC deficiencies tend to have elevated ammonia levels.
- V. Nucleotide replacement has been the mainstay of treatment of HOA. Case reports document rapid hematologic response with administration of uridine. Some patients treated with uridine have reached adulthood and some who have been treated with uridine lifelong have fathered or given birth to normal children. Supportive therapies include blood transfusions, intravenous hydration and electrolyte replacement, and treatment for renal and infectious disease complications.
- VI. FDA approval of uridine triacetate (Xuriden) was based on collective evidence from case reports, pharmacokinetic studies, safety studies, and one Phase III, open-label, single-arm, six-week clinical

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trial and its six-month extension phase. The efficacy was evaluated in a Phase III trial which enrolled four patients with HOA (three male, one female; age range three to 19 years). Three patients were previously treated with uridine and were switched to uridine triacetate (Xuriden). One patient was treatment naïve. The study evaluated stability or improvement in patients' hematologic parameters in the initial six-week period and the extension phase. By week six, three previously treated patients met the primary endpoint and maintained stability of their hematologic parameters, while one treatment naïve patient failed to meet the primary endpoint – improvement in hematologic parameters. The secondary endpoint was improved growth parameters (height and weight). Effect on growth was assessed in three patients and remained unchanged after 24 months of treatment.

- VII. Uridine triacetate (Xuriden) is the only FDA approved therapy for HOA. The National Organization for Rare Disease Disorders and other expert opinions recommend treatment with uridine triacetate (Xuriden).
- VIII. Uridine triacetate (Xuriden) should not be used for the treatment of fluoropyrimidine overdose/overexposure. A different formulation of uridine triacetate (Vistogard) has been approved by the FDA for the treatment of this condition.

Investigational or Not Medically Necessary Uses

- I. Uridine triacetate (Xuriden) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Fluoropyrimidine overdose/overexposure

References

1. Xuriden [Prescribing Information]. Wellstat Therapeutics Corporation: Rockville, MD. September 2015.
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Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	01/2021

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP223

Split Fill Management*

Description

Vandetanib (Caprelsa) is an orally administered kinase inhibitor, with activity at VEGF, EGFR, and RET kinases.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
vandetanib (Caprelsa)	100 mg tablets	Locally advanced or metastatic medullary thyroid cancer	60 tablets/30 days
	300 mg tablets		30 tablets/30 days

Initial Evaluation

- I. Vandetanib (Caprelsa) may be considered medically necessary when the following criteria are met:
 - A. Member is 18 years of age or older; **AND**
 - B. Medication is prescribed by, or in consultation with, an oncologist or endocrinologist; **AND**
 - C. A diagnosis of **unresectable locally advanced or metastatic (stage III or IV) medullary thyroid cancer** when the following is met:
 1. Medication is not used in combination with any other oncology therapy.
- II. Vandetanib (Caprelsa) is considered investigational when used for all other conditions, including but not limited to:
 - A. Anaplastic Thyroid Carcinoma
 - B. Biliary tract cancer
 - C. Breast cancer
 - D. Follicular Thyroid Carcinoma
 - E. Glioblastoma
 - F. Ovarian cancer
 - G. Renal cell carcinoma
 - H. Urothelial cancer
 - I. Non-small cell lung cancer

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Medication is prescribed by, or in consultation with, an oncologist or endocrinologist; **AND**
- IV. Will not be used with any other oncology therapy; **AND**
- V. Disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread.

Supporting Evidence

- I. Vandetanib (Caprelsa) is a kinase inhibitor with activity at multiple kinases. *In vitro* studies show that vandetanib (Caprelsa) inhibits the activity of epidermal growth factor receptor (EGFR) family, vascular endothelial growth factor (VEGF) receptors, rearranged during transfection (RET), protein tyrosine kinase 6, TIE2, members of the EPH receptors kinase family, and members of the Src family of tyrosine kinases. In mouse models, vandetanib (Caprelsa) reduced tumor cell growth and metastasis.
- II. Vandetanib (Caprelsa) was studied in a Phase 3, double blind, placebo controlled, randomized trial (ZETA) in 331 patients with symptomatic or progressive unresectable locally advanced or metastatic medullary thyroid cancer. There is currently no evidence that it is safe and effective in treating other types of cancer.
- III. The ZETA trial evaluated treatment with vandetanib (Caprelsa) as monotherapy versus placebo. Patients in the trial had either hereditary, sporadic, or unknown, or metastatic disease type. Fifty nine percent of patients had a RET positive mutation while 40% had unknown RET mutation. Patients were excluded from treatment if they had significant cardiac, hematopoietic, hepatic, or renal dysfunction, were treated with chemotherapy and/or radiation therapy within four weeks of treatment with vandetanib (Caprelsa) or were taking any concomitant medications that may have affected QTc or induced CYP3A4 function.
- IV. The primary endpoint evaluated in the ZETA trial was progression free survival (PFS). There was a statistically significant improvement in PFS for patients randomized to vandetanib (Caprelsa). The number of events in vandetanib (Caprelsa) arm was 59 (26%) and 41 (41%) in the placebo arm with a Hazard Ratio (HR) = 0.35; 95% Confidence Interval (CI) = 0.24-0.53; $p < 0.001$. The median survival in months for the placebo arm was 16.4 while for the vandetanib (Caprelsa) arm the median survival was not reached at the time of analysis; however, the predicted median survival was 30.5 months. The mature data for overall survival (OS) was studied as a secondary endpoint and was similar between both treatment arms at 81.6 months for vandetanib (Caprelsa) and 80.4 months for placebo arm. However, OS survival data was not powered and was confounded by patients from the placebo arm that were eligible to start treatment with vandetanib (Caprelsa) after conclusion of the study. Other secondary endpoints evaluated included objective response rate (ORR) and disease control rate, both of which reached

statistical significance when compared to placebo. Quality of life and pain reduction outcomes were not reported or could not be evaluated.

- V. Fifty-five percent (55%) of the patients on the vandetanib (Caprelsa) arm experienced grade 3 or 4 adverse events. Adverse reactions resulting in death occurred in five patients treated with vandetanib (Caprelsa) due to respiratory failure, respiratory arrest, aspiration pneumonia, cardiac failure with arrhythmia, and sepsis. Causes of discontinuation in vandetanib (Caprelsa)-treated patients in >1 patient included asthenia, fatigue, rash, arthralgia, diarrhea, hypertension, prolonged QT interval, increase in creatinine, and pyrexia. Serious adverse events in vandetanib (Caprelsa) treated patients in >2% of patients included diarrhea, pneumonia, and hypertension. Patients receiving vandetanib (Caprelsa) experienced a mean prolongation of their QT interval of 35ms, and sudden death and torsades des pointes have been observed with vandetanib (Caprelsa). A Risk Evaluation and Mitigation Strategy (REMS) is used to decrease the risk of these adverse events.
- VI. Vandetanib (Caprelsa) has a Category 1 recommendation by the National Comprehensive Cancer Network (NCCN) guidelines for the treatment of recurrent or persistent medullary thyroid carcinoma and joins cabozantinib (Cabometyx) and selipergatinib (Retevmo) in the list of preferred systemic regimens. It is also recommended as the first line treatment option by the American Thyroid Association Guidelines. Vandetanib (Caprelsa) should be prescribed in consultation with, or by, an oncologist or endocrinologist for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease. Use of vandetanib (Caprelsa) in patients with indolent, asymptomatic, or slowly progressive disease should only be considered after examining the treatment related risks of this agent.

Investigational or Not Medically Necessary Uses

- I. Vandetanib (Caprelsa) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Anaplastic Thyroid Carcinoma
 - B. Biliary tract cancer
 - C. Breast cancer
 - D. Follicular Thyroid Carcinoma
 - E. Glioblastoma
 - F. Ovarian cancer
 - G. Renal cell carcinoma
 - H. Urothelial cancer
 - I. Non-small cell lung cancer

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

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1. Caprelsa (vandetanib) [package insert]. Cambridge, MA: Sanofi Genzyme; December 2016.
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Policy Implementation/Update:

Action and Summary of Changes	Date
Policy was updated and transitioned from an old criteria to a new format Removal of criteria requirements that are managed by provider (drug-drug interactions, REMS program, monitoring of CrCl, QT prolongation, hepatic impairments, hypertension, and other aspects from labeled warnings and precautions)	02/2021
Criteria created	02/2012

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP071

Description

Venetoclax (Venclexta) is an orally administered B-cell lymphoma-2 (BCL-2) inhibitor.

Length of Authorization

- Initial:
 - i. Previously untreated CLL/SLL: 12 months
 - ii. All other indications: Six months
- Renewal:
 - i. Previously untreated CLL/SLL: Cannot be renewed
 - ii. All other indications: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
venetoclax (Venclexta)	Starter Pack	Chronic lymphocytic leukemia (CLL); Small lymphocytic lymphoma (SLL)	1 pack/28 days
	10 mg tablets		28 tablets/28 days
	50 mg tablets		28 tablets/28 days
	100 mg tablets		120 tablets/30 days
	100 mg tablets	Acute myeloid leukemia	180 tablets/30 days

Initial Evaluation

- I. Venetoclax (Venclexta) may be considered medically necessary when the following criteria below are met:
 - A. Prescribed by, or in consultation with, an oncologist or hematologist; **AND**
 - B. A diagnosis of:
 1. **Relapsed/refractory chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL); AND**
 - i. Received at least one prior therapy [e.g., Imbruvica (ibrutinib) or chemotherapy-containing regimen]; **AND**
 - ii. Will be used as monotherapy or in combination with rituximab (Rituxan); **OR**
 2. **Previously untreated chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL); AND**
 - i. Will be used in combination with obinutuzumab (Gazyva); **OR**
 3. **Newly-diagnosed acute myeloid leukemia (AML); AND**
 - i. Age 75 years and older; **OR**
 - ii. Have comorbidities that preclude use of intensive induction chemotherapy such as:

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- a. Baseline Eastern Cooperative Oncology Group (ECOG) performance status of 2-3
 - b. Severe cardiac or pulmonary comorbidity
 - c. Moderate hepatic impairment
 - d. CrCL ≥ 30 to < 45 mL/min; **AND**
 - iii. Used in combination with azacitidine or decitabine or low-dose cytarabine
- II. Venetoclax (Venclexta) is considered investigational for all other conditions, including but not limited to:
 - A. Acute Myeloid Leukemia – Previously treated
 - B. Multiple Myeloma (MM)
 - C. Previously untreated CLL/SLL – Treatment for more than 12 months

Renewal Evaluation

- I. Member has a diagnosis of relapsed/refractory CLL/SLL or newly diagnosed AML; **AND**
- II. Clinical documentation of response to treatment, such as stabilization or improvement of disease; **AND**
- III. Absence of unacceptable toxicity from the medication

Supporting Evidence

- I. Venetoclax (Venclexta) is FDA-approved for the treatment of CLL/SLL, in adult patients with or without 17p deletion.
- II. Patients included in venetoclax (Venclexta) monotherapy studies in CLL/SLL were relapsed/refractory to fludarabine-based regimens (e.g. Rituximab+Fludarabine+Cyclophosphamide, Fludarabine+Rituximab, Fludarabine+Cyclophosphamide) or alkylator- based regimens (e.g. chlorambucil, bendamustine), or to ibrutinib (Imbruvica) or idelalisib (Zydelig). Patients included in the venetoclax (Venclexta) plus rituximab (Rituxan) trial (MURANO) for relapsed CLL/SLL had received one to three previous treatments (including at least one chemotherapy-containing regimen). Prior radiation therapy or stem cell transplant alone is not considered a prior therapy as this treatment strategy alone was not considered an inclusion in pivotal trials.
- III. Venetoclax (Venclexta) approval in untreated CLL/SLL was based on the findings from the CLL14 randomized, open label, phase 3 trial. CLL14 evaluated the safety and efficacy of fixed-duration treatment with venetoclax (Venclexta) in combination with obinutuzumab (VEN+G) versus obinutuzumab in combination with chlorambucil (GCLb) for patients with previously untreated CLL with coexisting medical conditions. Patients received 12 months of venetoclax (Venclexta) in combination with six cycles of obinutuzumab. The trial met its primary outcome of progression-free survival (PFS) in patients treated with Venclexta plus obinutuzumab compared to patients who received chlorambucil plus obinutuzumab, a commonly used standard of care. After a median follow-up of 28 months, Venclexta plus obinutuzumab reduced the risk of progression or death by 67% compared with chlorambucil plus obinutuzumab (hazard ratio: 0.33, 95%

confidence interval [CI]: 0.22, 0.51; $p < 0.0001$). The majority of patients receiving Venclexta in the trial remained progression-free at two years.

- IV. FDA granted accelerated approval to venetoclax (Venclexta) for use in combination with azacitidine or decitabine or low-dose cytarabine for the treatment of adult patients with newly-diagnosed acute myeloid leukemia (AML) who are aged 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy. Initial FDA-approval was based on two phase Ib/II trials in this setting. The findings from these trials were consolidated by phase III confirmatory studies (VIALE-A and VIALE-C).
- V. Venetoclax (Venclexta) was studied in a confirmatory phase III randomized (2:1) double-blind, placebo-controlled trial (VIALE-A), which assessed the efficacy and safety of venetoclax (Venclexta) in combination with azacitidine (IV or SQ administration) versus placebo+ azacitidine ($n = 431$). Participants in this trial had median age of 76 years, intermediate or poor/ high risk AML and at least one comorbidity precluding intensive therapies. At median duration of follow-up (20.5 months, $< 0.1 - 30.7$), median overall survival for venetoclax- azacitidine treatment arm was 14.7 months (95% CI; 11.9, 18.7) as compared to that of 9.6 months (95% CI; 7.4, 12.7) for placebo-azacitidine arm (HR 0.66; 95% CI; 0.52-0.85; $p < 0.0001$). Additionally, treatment arm (venetoclax- azacitidine) also reported complete remission in 66.4% (95% CI; 60.6, 71.9) versus 28.3% (95% CI; 21.1, 36.3) in placebo-azacitidine arm ($p < 0.001$) with 43.4% participants achieving composite complete remission before cycle 2.
- VI. In VIALE-C clinical trial, efficacy and safety of venetoclax (Venclexta) in combination with low-dose cytarabine (LDAC) was compared with placebo plus LDAC in an ongoing double-blind, randomized (2:1) phase 3 study. From a pool of 211 randomized study participants ($n = 143$ in treatment arm versus $n = 68$ in placebo arm), median follow-up of 17.5 months (95% CI; 0.1, 23.5) was reported at data cut-off. Median overall survival (OS) was 8.4 months in the treatment (venetoclax-cytarabine) arm versus 4.1 months in placebo-cytarabine arm (HR 0.70; 95% CI 0.50–0.99; $P = 0.04$). This OS data was not statistically significant. Additionally, a median event-free survival (EFS) was reported at 4.9 months vs 2.1 months for treatment and placebo arms, respectively (HR 0.61; 95% CI; 0.44, 0.84; $P = 0.003$).

Investigational or Not Medically Necessary Uses

- I. Acute Myeloid Leukemia – Previously treated
 - A. Pivotal trials leading to FDA approval were specifically in the previously untreated setting. Use in the relapsed/refractory setting is not supported by clinical trials nor cited within NCCN AML guidelines.
- II. Multiple Myeloma (MM)
 - A. Venetoclax (Venclexta) is currently being evaluated for use in MM and is the subject of ongoing clinical trials. As of March 2019, “FDA reviewed data from the BELLINI clinical trial (NCT02755597, Study M14-031) evaluating the use of Venetoclax (Venclexta) combined with bortezomib and dexamethasone in patients with multiple myeloma. The interim trial results demonstrated an increased risk of death for patients receiving Venetoclax (Venclexta) as compared to the control group. On March 6, 2019, the FDA required no new patients be enrolled on the Bellini trial. The FDA suspended enrollment in other ongoing multiple myeloma clinical trials of Venclexta.”

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III. Previously untreated CLL/SLL – Treatment for more than 12 months

- A. Venetoclax (Venclexta) approval in untreated CLL/SLL was based on the findings from the CLL14 randomized, open label, phase 3 trial. CLL14 evaluated the safety and efficacy of fixed-duration treatment with venetoclax (Venclexta) in combination with obinutuzumab (VEN+G) versus obinutuzumab in combination with chlorambucil (GClb). Patients received 12 months of venetoclax (Venclexta) in combination with six cycles of obinutuzumab. Treatment beyond 12 months has not been evaluated.

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Policy Implementation/Update:

Action and Summary of Changes	Date
Updated supporting evidence for venetoclax phase III confirmatory clinical trials for newly diagnosed acute myeloid leukemia (AML)	12/2020
Added new FDA approval in untreated CLL/SLL in combination with obinutuzumab (Gazyva)	06/2019
Added new FDA approval in Acute Myeloid Leukemia.	12/2018
Included new FDA expanded indication in CLL/SLL without 19p deletion and expanded initial approval to 6 months.	08/2018

Policy Type: PA

Pharmacy Coverage Policy: UMP224

Description

Vericiguat (Verquvo) is an orally administered guanylate cyclase stimulator.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
vericiguat (Verquvo)	2.5 mg tablets	Reduce the risk of cardiovascular death and heart failure (HF) hospitalization following a hospitalization for HF or need for outpatient IV diuretics in adults with symptomatic chronic HF and ejection fraction less than 45%	30 tablets/30 days
	5 mg tablets		
	10 mg tablets		

Initial Evaluation

- I. Vericiguat (Verquvo) may be considered medically necessary when the following criteria are met:
 - A. Member is 18 years of age or older; **AND**
 - B. Medication is prescribed by, or in consultation with, a cardiologist; **AND**
 - C. A diagnosis of **chronic heart failure with reduced ejection fraction (HFrEF)** when the following are met:
 1. Member has HFrEF defined as New York Heart Association functional class II, III, or IV; **AND**
 2. Member has a documented reduced left ventricular ejection fraction of less than 45%; **AND**
 3. Provider attestation that member has recent evidence of worsening heart failure as defined by ONE of the following:
 - i. Hospitalization for heart failure within the last six months; **OR**
 - ii. Receiving intravenous (IV) diuretic therapy, within the last three months;
 - AND**
 4. Member is being treated with one agent from each of the following groups unless ineffective, contraindicated or not tolerated:
 - i. Group 1: Beta-blocker (e.g., metoprolol succinate, carvedilol, bisoprolol)

- ii. Group 2: ACE-I/ARB (e.g., lisinopril, losartan, valsartan, ramipril) OR ARNI (i.e. sacubitril/valsartan)
 - iii. Group 3: Mineralocorticoid antagonist (e.g., spironolactone)
- II. Vericiguat (Verquvo) is considered investigational when used for all other conditions, including but not limited to:
 - A. Heart failure with preserved ejection fraction (HFpEF)

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Member has exhibited improvement or stability of disease symptoms; **OR**
- IV. In the absence of improvement or stability of disease symptoms, the provider attests continuation of therapy is medically necessary AND clinical rationale of medical necessity has been provided and reviewed by a Moda Health clinician.

Supporting Evidence

- I. Vericiguat (Verquvo) was studied in one randomized, double-blind, placebo-controlled Phase 3 (VICTORIA) trial in 5,050 patients with chronic heart failure (NYHA functional class II, III or IV) with a reduced ejection fraction (<45%), evidence of recent decompensation or worsening heart failure, defined as recent hospitalization for heart failure in the last three months, hospitalization in the last three to six months, or receiving intravenous (IV) diuretic therapy, without hospitalization, within the last six months.
- II. The primary efficacy outcome was a composite endpoint of death from cardiovascular causes or first hospitalization for heart failure. The primary endpoint was achieved by 897 patients (35.5%) in the vericiguat group and 972 patients (38.5%) in the placebo group (hazard ratio, 0.90; 95% CI 0.82 to 0.98; P=0.02).
- III. Adverse events occurred in 80.5% of patients receiving vericiguat (Verquvo) with serious adverse events occurring in 32.8% of those patients. Notable side effects observed during the clinical trial include symptomatic hypotension (9.1% patients in vericiguat group vs. 7.9% in placebo group) and syncope (4.0% patients in vericiguat group vs. 3.5% in placebo group). Anemia developed in 7.6% patients in the vericiguat group compared to 5.7% patients in the placebo group. Of those developing anemia, 1.6% cases in the vericiguat group and 0.9% in the placebo group were considered serious adverse events.
- IV. The 2017 AHA/ACC/HFSA guidelines recommend first-line therapy with an ACE-I or ARB and a guideline directed beta blocker (bisoprolol, carvedilol or metoprolol succinate) with use of diuretics as needed for symptom management. Spironolactone, sacubitril/valsartan, isosorbide

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dinitrate, hydralazine, and ivabradine can be used as adjunct therapy to first-line agents based on patients NYHA functional class and other specified patient characteristics. In the VICTORIA trial, 60% of patients received triple therapy with a beta blocker, ACE-I/ARB/ARNI, and mineralocorticoid antagonist in addition to the study drug.

- V. Vericiguat (Verquuo) was studied in adult patients age 18 and older and has not been evaluated for safety and/or efficacy in pediatric patients.

Investigational or Not Medically Necessary Uses

- I. Vericiguat (Verquuo) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Heart failure with preserved ejection fraction (HFpEF)
 - i. Vericiguat (Verquuo) was studied in two phase 2b trials, SOCRATES-PRESERVED and VITALITY-HFpEF, in the setting of chronic heart failure with preserved ejection fraction. The primary efficacy endpoints of change in baseline in log-transformed N-terminal pro-B-type natriuretic peptide (NT-ProBNP) and left atrial volume (LAV) and change in the Kansas City Cardiomyopathy Questionnaire (KCCQ) PLS quality index, respectively, were not met for either study and phase III studies were not pursued.

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Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	02/2021

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP072

Description

Vigabatrin's (Sabril, Vigadrone, Vigafyde) full mechanism of action is unknown at this time; however, it is an orally administered agent that has irreversible inhibition of gamma-aminobutyric acid transaminase (GABA-T).

Length of Authorization

- Initial:
 - Complex Partial Epileptic Seizure: Three months
 - West Syndrome (Infantile Spasms): One month
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
vigabatrin (Sabril)	500mg tablets	Refractory complex partial epileptic seizure, adjunct therapy	180 tablets/30 days
Vigabatrin (Sabril, Vigadrone)	500mg/packet powder for oral suspension		180 packets/30 days
		West Syndrome (infantile spasms)	120 packets/30 days
Vigabatrin (Vigafyde)	100 mg/mL solution	Infantile spasms in pediatric patients	750mL/30 days

Initial Evaluation

- I. **Vigabatrin (Sabril, Vigadrone, Vigafyde)** may be considered medically necessary when the following criteria below are met:
 - A. Medication is prescribed by, or in consultation with, a neurologist; **AND**
 - B. The member has had an ophthalmologic examination prior to initiating vigabatrin (Sabril, Vigadrone, Vigafyde) or will be examined no later than four weeks after initiation of therapy; **AND**
 1. Provider attestation that the member will have an ophthalmologic examination at least every three months during treatment; **OR**
 - C. The member is blind prior to initiation of therapy; **AND**
 - D. Request is for generic vigabatrin or vigabatrin (Vigadrone); **OR**
 1. Request is for branded vigabatrin formulation (Sabril, Vigafyde); **AND**
 2. Documentation of clinical rationale stating why generic vigabatrin or vigabatrin (Vigadrone) is not appropriate or is contraindicated; **AND**
 - E. A diagnosis of one of the following:
 1. **Complex partial epileptic seizure (focal onset impaired awareness seizure); AND**
 - i. Vigabatrin (Sabril, Vigadrone) will be used in combination with at least one other anti-epileptic medication (i.e., used as adjunct therapy) such as

- carbamazepine, phenytoin, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate, divalproex sodium, zonisamide, tiagabine; **AND**
 - ii. A trial and failure of at least two anti-epileptic medications listed above; **AND**
 - iii. Member is two years of age or older; **OR**
 - 2. **West Syndrome (Infantile Spasms); AND**
 - i. Member is between one month and two years of age; **AND**
 - ii. The prescribed dose does not exceed 150 mg/kg/day
- II. Vigabatrin (Sabril, Vigadrone) is considered investigational when used for all other conditions, including but not limited to:
 - A. Seizures that are not considered complex partial epileptic or focal onset impaired awareness seizures
 - B. Tourette's disorder
 - C. Substance abuse (e.g., cocaine, methamphetamine, alcohol dependence)
 - D. Autoimmune encephalitis

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Provider attestation that ophthalmologic examination has been completed every three months since initiation of therapy; **AND**
- IV. Generic vigabatrin OR vigabatrin (Vigadrone) is prescribed, or documentation is provided, regarding clinical rationale as to why generic vigabatrin or vigabatrin (Vigadrone) is not appropriate or is contraindicated **AND**
- V. A reduction in the severity or frequency of seizures or spasms; **AND**
 - A. **Complex partial epileptic seizure (focal onset impaired awareness seizure); AND**
 - 1. The medication continues to be used in combination with at least one other anti-epileptic medication (i.e., used as adjunct therapy) such as carbamazepine, phenytoin, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate, divalproex sodium, zonisamide, tiagabine; **OR**
 - B. **West Syndrome (Infantile Spasms); AND**
 - 1. Clinical benefit has been assessed and documented within the first two to four weeks of treatment (please note: extensions will not be given if assessment has not taken place within four weeks of treatment initiation); **AND**
 - 2. The prescribed dose does not exceed 150 mg/kg/day

Supporting Evidence

- I. Vigabatrin (Sabril, Vigadrone, Vigafyde) has a black box warning for permanent vision loss, and those who take the medication are at risk for vision loss with any amount of medication. The risk

increases with greater doses and duration of vigabatrin (Sabril, Vigadrone, Vigafyde) administration. This medication is available through a Risk Evaluation Mitigation Strategy (REMS) Program, and a specialist will need to be involved in prescribing to ascertain if the benefits of vigabatrin (Sabril, Vigadrone, Vigafyde) outweigh the risk of vision loss.

- II. Recommended ophthalmologic monitoring should start at baseline or within four weeks of initiating therapy, every three months during therapy, and through three to six months post discontinuation.
- III. Vigabatrin (Sabril, Vigadrone) is FDA-approved for the treatment of complex partial epileptic seizures (focal onset impaired awareness seizure) for ages two years and older while vigabatrin (Sabril, Vigadrone, Vigafyde) is FDA-approved for the treatment of West Syndrome (infantile spasms) for ages one month to two years. Given the complexities of diagnosing and treating these conditions, supervision of treatment by a neurologist is required.

Complex Partial Epileptic Seizure

- IV. In complex partial epileptic seizure, the medication is FDA-approved in the refractory setting after failure of other therapies and should be used in addition to at least one other anti-epileptic (i.e., vigabatrin [Sabril, Vigadrone] is an adjunct therapy).
- V. Vigabatrin (Vigadrone) is an AA-rated authorized generic of Sabril and is fully substitutable for both Sabril and generic vigabatrin 500mg/packet for oral solution.
- VI. The max dose of vigabatrin (Sabril, Vigadrone) is 3,000 mg/day for complex partial epileptic seizure and a maximum of 150 mg/kg/day for West Syndrome.

West Syndrome (infantile spasms)

- I. Infantile spasms are an age-specific subset of epileptic spasms confirmed by electroencephalography (EGG). A majority of affected individuals will present at less than one year of age (between three and twelve months).
- II. Vigabatrin formulations are FDA approved as monotherapy for the treatment of infantile spasms in pediatric patients 1 month to 2 years of age for whom the potential benefits outweigh the potential risk of vision loss.
- III. For West Syndrome, significant clinical benefit should be realized within four weeks of therapy initiation per consensus statements, and the medication should be discontinued if benefit is not realized. Due to the risks associated with the medication, continuation of therapy will not be granted in absence of clinical benefit.

Investigational or Not Medically Necessary Uses

All indications listed below have not been sufficiently studied for safety and efficacy or have inconclusive evidence for use of vigabatrin (Sabril, Vigadrone).

- I. Seizures that are not considered complex partial epileptic or focal onset impaired awareness seizures
- II. Tourette's disorder
- III. Substance abuse (e.g., cocaine, methamphetamine, alcohol dependence)
- IV. Autoimmune encephalitis

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Policy Implementation/Update:

Action and Summary of Changes	Date
Updated policy name. Added criteria to step branded vigabatrin formulations (Sabril, Vigafyde) through generic formulations (generic vigabatrin, Vigadrone). Updated supporting evidence for infantile spasms.	08/2025
Added Vigafyde solution to QL table	08/2024
Updated minimum age for use as adjunct therapy for refractory complex seizures to age two and older to align with FDA-label age-expansion; Added Vigadrone packets to policy	03/2021
Date created	03/2019

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP198

Split Fill Management*

Description

Vismodegib (Erivedge) is an orally administered hedgehog pathway inhibitor.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
vismodegib (Erivedge)	150 mg capsules	Basal cell carcinoma; metastatic or locally advanced	28 capsules/28 days

Initial Evaluation

- I. Vismodegib (Erivedge) may be considered medically necessary when the following criteria are met:
 - A. Member is 18 years of age or older; **AND**
 - B. Medication is prescribed by, or in consultation with, an oncologist or dermatologist; **AND**
 - C. Vismodegib (Erivedge) will NOT be used in combination with any other oncologic medication; **AND**
 - D. Member has not progressed on any other oncologic medication (e.g. has not progressed on sonidegib [Odomzo]); **AND**
 - E. A diagnosis of **basal cell carcinoma (BCC)** when the following are met:
 1. Member has metastatic (Stage IV) basal cell carcinoma; **OR**
 2. Member has locally advanced basal cell carcinoma; **AND**
 - i. Basal cell carcinoma has recurred or progressed after radiation or surgery; **OR**
 - ii. Member is not a candidate for either
- II. Vismodegib (Erivedge) is considered investigational when used for all other conditions, including but not limited to:
 - A. Ovarian Cancer
 - B. Nevoid basal cell carcinoma syndrome
 - C. Prostate Cancer
 - D. Acute leukemia

- E. Lymphoma
- F. Breast Cancer
- G. Medulloblastoma
- H. Multiple myeloma
- I. Myelofibrosis
- J. Graft versus host disease
- K. Pancreatic cancer
- L. Lung cancer
- M. Hepatocellular carcinoma

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Vismodegib (Erivedge) is prescribed by, or in consultation with, an oncologist or dermatologist; **AND**
- IV. Member has a diagnosis of **metastatic or locally advanced basal cell carcinoma; AND**
- V. Member has experienced a clinical response to therapy defined by improvement or stabilization of disease or decrease or stabilization of tumor size or spread; **AND**
- VI. Provider attestation that the member, either male or female, has been counseled on the teratogenicity and embryo-fetal toxicity risks with vismodegib (Erivedge).

Supporting Evidence

- I. The safety and efficacy of vismodegib (Erivedge) in basal-cell carcinoma was evaluated in the pivotal ERIVANCE trial; a multicenter, international, two-cohort, open-label, single-arm study of 104 patients with metastatic basal-cell carcinoma (BCC) and those with locally advanced BCC who had inoperable disease or who were not a candidate for surgery. Patients with locally advanced disease were required to have had prior radiation therapy, unless contraindicated or inappropriate.
- II. The primary efficacy endpoint was the independently assessed objective response rate (ORR) based on RECIST guidelines for metastatic disease or a decrease of 30% or more in the externally visible or radiographic dimension or complete resolution of ulceration for locally advanced disease. The key secondary endpoint was duration of response (DOR). The study met its primary endpoint in both cohorts with an ORR of 30% (95% confidence interval [CI], 16 to 48; P=0.001) in the group with metastatic BCC and 43% (95% CI, 30 to 56; P<0.001) in the group with locally advanced BCC. The median duration of objective response was 7.6 months for metastatic BCC (rang, 2.1 to 11.1) and locally advanced BCC (range, 1.0 to 12.9).
- III. During the ERIVANCE trial, all patients experienced at least one adverse event (AE), with the majority classified as grade 1 or 2 in severity, and 25% experienced at least one serious adverse event. Of those who experienced a serious adverse event, seven patients experienced a fatal

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- adverse event and 12% had an adverse event that led to discontinuation. Common adverse events included muscle spasms, dysgeusia, alopecia, fatigue and weight loss.
- IV. Patients enrolled in the study were age 18 and older and concurrent antitumor (oncologic) therapy was not permitted. The safety and/or efficacy of use in pediatric and adolescent patients or in combination with other oncologic therapies has not been evaluated.
 - V. Vismodegib (Erivedge) carries a black box warning for Embryo-fetal toxicity, as this agent is known to cause embryo-fetal death or severe birth defects when administered to a pregnant woman. FDA-label advises women of reproductive potential and men to use effective contraception during therapy with vismodegib (Erivedge) and for 24 months after the final dose.
 - VI. Long-term safety and efficacy of vismodegib (Erivedge) was evaluated in a follow-up study of the ERIVANCE trial for 39 months after the final data cutoff date of the primary analysis. The primary end point was ORR, with key secondary endpoints including DOR and overall survival (OS). Of the 104 patients enrolled at baseline, 96 discontinued for the following reasons: disease progression (27.9%), patient decision to withdraw (26.0%), and AEs (21.9%). The ORR for the mBCC cohort was 48.5% [95% CI, 30.8-66.2] and 60.3% in the laBCC cohort [47.2-71.7]. Median DOR was 14.8 months for the mBCC cohort [7.4-16.6] with a median OS of 33.4 months; Median DOR was 26.2 months [9.0-37.6] and OS was not estimable.
 - VII. No new safety concerns arose during the follow-up study. Again, all patients enrolled in the study experienced one or more treatment emergent adverse events (TEAEs). The incidence of TEAEs increased between the time of the primary analysis and the final data cutoff date for the follow-up study and correlated with patients who had 12 or more months of exposure to vismodegib (Erivedge). Patients who received treatment for 12 months or more had higher rates of muscle spasms, alopecia, dysgeusia, weight decreased, fatigue, and nausea. Deaths occurring during the study were considered by the investigator to be related to vismodegib (Erivedge).
 - VIII. Vismodegib (Erivedge) is currently recommended by NCCN guidelines for use in recurrent or advanced disease, with the caveat to be used in the FDA-approved indication of metastatic or locally advanced disease, with a category 2A recommendation.
 - IX. Vismodegib (Erivedge) is FDA-approved for adults with metastatic and locally advanced basal cell carcinoma. Vismodegib (Erivedge) has an overlapping indication with sonidegib (Odomzo), and if disease progression has occurred on or after one of these therapies, there is currently insufficient evidence regarding safety and/or efficacy of the other. One published piece of literature evaluated sonidegib (Odomzo) in those that were resistant to vismodegib (Erivedge); however, this trial included only nine subjects all of which showed no response to sonidegib (Odomzo) or were not evaluable for safety and/or efficacy. Available evidence disfavors use of sequential Hedgehog pathway inhibitors.

Investigational or Not Medically Necessary Uses

- I. Vismodegib (Erivedge) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Ovarian Cancer
 - B. Nevroid basal cell carcinoma syndrome
 - C. Prostate Cancer

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- D. Acute leukemia
- E. Lymphoma
- F. Breast Cancer
- G. Medulloblastoma
- H. Multiple myeloma
- I. Myelofibrosis
- J. Graft versus host disease
- K. Pancreatic cancer
- L. Lung cancer
- M. Hepatocellular carcinoma

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References

1. Vismodegib (Erivedge) [Prescribing Information]. Genentech USA, INC. South San Francisco, CA. January 2012.
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5. Danial C., Sarin K. Oro A., et al. An investigator-initiated open-label trial of sonidegib in advanced basal cell carcinoma patients resistant to vismodegib. *Clin Cancer Res*. 2016;22: 1325-1329.

Policy Implementation/Update:

Action and Summary of Changes	Date
Transition to policy format, addition of supporting evidence, addition of requirement attesting agent will NOT be used in combination with any other oncologic medication, removal of teratogenicity counseling attestation.	10/2020
Previous review	01/2013 12/2012
Criteria created	07/2012

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP232

Split Fill Management*

Description

Voclosporin (Lupkynis) is an orally administered calcineurin-inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
voclosporin (Lupkynis)	7.9 mg capsules	Lupus Nephritis	180 capsules/30 days

Initial Evaluation

- I. **Voclosporin (Lupkynis)** may be considered medically necessary when the following criteria below are met:
 - A. Member is 18 years of age or older; **AND**
 - B. Medication is prescribed by, or in consultation with, a rheumatologist or nephrologist; **AND**
 - C. **Not** used in combination with biologic(s) [e.g., rituximab (Rituxan), abatacept (Orencia), belimumab (Benlysta)]; **AND**
 - D. A confirmed positive autoantibody test [antinuclear (ANA) and/or anti-double-stranded DNA (anti-ds-DNA)]; **AND**
 - E. A diagnosis of **Lupus Nephritis (LN)**; **AND**
 1. Biopsy indicating class III (focal), IV (diffuse), or V (membranous) LN; **AND**
 2. Biopsy shows active lesions; **OR**
 - i. Biopsy shows active AND chronic lesions; **AND**
 3. Provider attestation indicating medication will be given in combination with mycophenolate (CellCept) for induction and maintenance; **AND**
 4. Provider attestation the member will continue to receive standard therapy (e.g., antimalarials, NSAIDs, immunosuppressives, corticosteroids), unless all are contraindicated or not tolerated; **AND**
 5. Treatment with belimumab (Benlysta) has been ineffective, contraindicated, or not tolerated.
- II. Voclosporin (Lupkynis) is considered investigational when used for all other conditions, including but not limited to:

- A. Systemic Lupus Erythematosus (SLE) with absence of lupus nephritis
- B. Severe active central nervous system lupus
- C. Renal transplantation

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. A diagnosis of **Lupus Nephritis (LN)**; **AND**
- IV. Member has exhibited improvement or stability of disease symptoms (e.g., reduction in proteinuria, improved/stable serum creatinine, reduction in urinary sediment); **AND**
- V. **Not** used in combination with other biologic(s) [e.g., rituximab (Rituxan), abatacept (Orencia), belimumab (Benlysta)]; **AND**
- VI. Member will continue to receive standard therapy (e.g., antimalarials, NSAIDs, immunosuppressives, corticosteroids), unless all are contraindicated or not tolerated.

Supporting Evidence

- I. LN is a kidney disease that develops in about 40% of patients with SLE. Approximately 10% of patients develop end stage renal disease (ESRD). Kidney failure, dialysis, and kidney transplants are common in this patient population. Patients with SLE with any sign of kidney involvement (glomerular hematuria and/or cellular casts, proteinuria >0.5 g/24 hours [or spot urine protein-to-creatinine ratio (UPCR) >500 mg/g], unexplained decrease in glomerular filtration rate (GFR)) are candidates for kidney biopsy to confirm diagnosis/class of LN, which then guides treatment.
 - Class I (minimal mesangial) and Class II (mesangial proliferative): Usually does not need specific immunosuppressive therapy but may be prone to histological transformation to more aggressive disease on repeat biopsy.
 - Class III (focal) and Class IV (diffuse): active, chronic classifications at high risk of developing ESRD, thus are targeted populations for immunosuppressive therapies.
 - Class V (membranous): presents similar to nephrotic syndrome with subendothelial deposits. Patients with Class III or IV disease may have these deposits and can be classified as Class III or IV in combination with Class V, can also present as pure Class V. Immunosuppressive therapy is indicated.
 - Class VI (advanced sclerosing): patients with sclerosing lesions; generally, do not respond to immunosuppressive therapy; treatment requires dialysis and/or kidney transplant.
- II. European Renal Association–European Dialysis and Transplant Association (EULAR/ERA–EDTA) 2019 and 2012 American College of Rheumatology guidelines on LN recommend immunosuppressive therapy for LN starting with an induction phase to achieve a renal response, which is recommended for the first six months of treatment, followed by maintenance therapy. Initial (induction) treatment is recommended with mycophenolate mofetil (MMF) or low-dose

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intravenous cyclophosphamide, both combined with glucocorticoids (pulses of IV methylprednisolone, then oral prednisone). Subsequent long-term maintenance treatment with MMF or azathioprine should follow, with no, or low-dose (< 7.5 mg/day), glucocorticoids. If a patient fails to respond to the first six months of induction therapy, guidelines suggest switching the immunosuppressive agent in combination with glucocorticoid pulse. Alternatively, calcineurin inhibitors (tacrolimus or cyclosporine) can be used as monotherapy or in combination with MMF as induction/maintenance therapy particularly in refractory cases.

- III. Guidelines recommend patients with LN be treated with hydroxychloroquine or an equivalent antimalarial, unless contraindicated, and adjunctive therapies be added to manage LN and attenuate complications of the disease.
- IV. The safety and efficacy of voclosporin (Lupkynis) in pediatric patients has not been established.
- V. The safety and efficacy of voclosporin (Lupkynis) in combination with biologic therapies [e.g., rituximab (Rituxan), abatacept (Orencia), belimumab (Benlysta)] has not been evaluated.
- VI. Per the package insert, use of voclosporin (Lupkynis) is not recommend in patients with a baseline eGFR less than or equal to 45 mL/min/1.73m² unless the benefit exceeds the risk, as these patients may be at increased risk for acute and/or chronic nephrotoxicity.
- VII. Policy is specific to list MMF as the induction/maintenance therapy due to potential safety concerns of additive toxic effects that may occur when co-administering voclosporin (Lupkynis) and cyclophosphamide. Per the package insert, use of voclosporin (Lupkynis) in combination with cyclophosphamide has not been established and is not recommended. The FDA review of voclosporin (Lupkynis) further adds “given the adverse reaction profile of cyclophosphamide and the lack of efficacy data for voclosporin in combination with cyclophosphamide, the review team concluded that there is reasonable concern about the benefit-risk profile in this situation, thus necessitating this limitation of use”.
- VIII. Voclosporin (Lupkynis) was evaluated as an adjunct to standard therapy in a Phase 3, randomized, double-blind, placebo-controlled, 52-week trial in adults (n=357) with biopsy proven LN. The primary efficacy outcome was complete renal response at week 52, defined as a UPCR < 0.5, eGFR ≥ 60 ml/min per 1.73 m² or a decline in no more than 20% from baseline, no rescue therapy, and a sustained dose ≤ than 10 mg of prednisone. The primary endpoint was met with 73 patients (40.8%) in the voclosporin (Lupkynis) arm achieving renal response compared to 40 patients (22.5%) in the placebo arm (odds ratio 2.7; 95% CI: 1.6-4.3; P<0.001).
 - All patients included in the trial were on background therapy with mycophenolate mofetil plus corticosteroids. Patients were 18 years of age and older with antibody positive SLE, ratio of urinary protein to creatinine (UPCR) of 2 or more (average patient had a baseline UPCR of 4), biopsy proven LN class III (focal lupus nephritis) or IV (diffuse lupus nephritis) with, or without, coexisting class V (membranous lupus nephritis), or pure class V lupus nephritis within last 6 months. All patients also had biopsy specimens showing active lesions or active and chronic lesions.
- IX. As of date there are no head to head trials comparing voclosporin (Lupkynis) to belimumab (Benlysta). Additionally, guidelines do not have recommendations around preferring either agent in the setting of LN. However, given the potential for chronic calcineurin inhibitor-related nephrotoxicity, especially relevant to this patient population with underlying renal disease, and the insufficient long-term controlled safety data beyond one year, the plan requires trial of or contraindication to belimumab (Benlysta) prior to use of voclosporin (Lupkynis).

Investigational or Not Medically Necessary Uses

- I. Voclosporin (Lupkynis) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Systemic Lupus Erythematosus (SLE) in absence of lupus nephritis (LN)
 - B. Severe active central nervous system lupus
 - C. Renal Transplantation

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References

1. Lupkynis [Prescribing Information]. Aurinia Pharma U.S., Inc.: Rockville, MD. January 2021.
2. Almaani S, Meara A, Rovin BH. Update on lupus nephritis. Clin J Am Soc Nephrol. 2017;12(5):825-835.
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4. Hahn BH, McMahon MA, Wilkinson A, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res (Hoboken). 2012;64(6):797-808.
5. Kidney Disease: Improving Global Outcomes (KDIGO) Glomerulonephritis Work Group. KDIGO Clinical Practice Guideline for Glomerulonephritis. Kidney inter., Suppl.2012;2: 139–27.
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Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2021

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP217

Split Fill Management*

Description

Vorinostat (Zolinza) is an orally administered inhibitor of histone deacetylase (HDAC) enzymes (HDAC1, HDAC2, HDAC3 and HDAC6).

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
Vorinostat (Zolinza)	100 mg capsules	Cutaneous T-Cell Lymphoma	120 capsules/30 days

Initial Evaluation

- I. Vorinostat (Zolinza) may be considered medically necessary when the following criteria are met:
 - A. Member is 18 years of age or older; **AND**
 - B. Medication is prescribed by, or in consultation with, an oncologist or a dermatologist; **AND**
 - C. Medication will not be used in combination with any other oncolytic agent; **AND**
 - D. Medication will not be used in combination with skin-directed therapies (e.g. Total Skin Electron Beam Therapy [TSEBT], phototherapy); **AND**
 - E. Member has not progressed on, or after, prior treatment with HDAC inhibitor (e.g. romidepsin [Istodax]); **AND**
 - F. A diagnosis of **cutaneous T-cell lymphoma (CTCL) [i.e. Sezary syndrome, mycosis fungoides]** when the following are met:
 1. Member has progressive (stage II or higher) or recurrent disease; **AND**
 2. Treatment with two or more of the following systemic regimens have been ineffective or not tolerated:
 - i. Systemic retinoid (e.g. bexarotene [Targretin])
 - ii. Methotrexate (oral or injectable)
 - iii. Systemic chemotherapy (e.g. chlorambucil, cyclophosphamide, etoposide)
 - iv. Targeted immunotherapy (e.g. mogamulizumab, brentuximab)
 - v. Interferons (e.g. peginterferon-alfa 2b [PegIntron], interferon gamma [Actimmune])

- II. Vorinostat (Zolinza) is considered investigational when used for all other conditions, including but not limited to:
 - A. Malignant pleural mesothelioma
 - B. Cutaneous B-cell lymphoma
 - C. Multiple myeloma
 - D. Hodgkin's lymphoma

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
- II. Medication is prescribed by, or in consultation with, an oncologist or a dermatologist; **AND**
- III. Member has experienced response to treatment (e.g. complete or partial remission, decrease from baseline in SWAT skin assessment scores, or PGA scores)

Supporting Evidence

- I. Vorinostat (Zolinza) is FDA-approved for the treatment of cutaneous manifestations in adult patients with cutaneous T-cell lymphoma (CTCL), who have progressive, persistent, or recurrent disease on, or following, 2 systemic therapies. Its approval was based on results from 2 single-arm, open-label trials. Efficacy and safety of vorinostat has not been studied in pediatric population.
- II. Sézary syndrome (SS) and mycosis fungoides (MF) are the most common subtypes of advanced cutaneous T cell lymphoma (CTCL). MF is a mature T cell non-Hodgkin lymphoma with presentation in the skin, but lymph nodes, blood, and viscera may also be involved. Skin lesions include erythroderma, patches, plaques, or tumors that may be localized or widespread. SS is a distinctive erythrodermic CTCL with leukemic involvement of malignant T cells that typically match the clone in the skin; less frequently, distinct clones may be detected in skin and blood.
- III. Advanced stage MF and SS are most often chronic with a persistent or relapsing course. The choice of therapy at different time points in the disease is largely dependent on the goals of therapy, which include long-term disease control and prompt symptom relief. Therefore, management of advanced and recurrent CTCL is often orchestrated by a multidisciplinary team comprised of dermatologists, medical oncologists, and radiation oncologists.
- IV. Patients with early stage CTCL are treated with skin-directed therapies. A randomized trial demonstrated that early aggressive therapy with combination chemotherapy plus total skin electron beam radiation therapy (TSEBT) does not appear to improve survival when compared with the use of sequential topical regimens. Skin directed therapies include topical corticosteroids, topical chemotherapy (nitrogen mustard or carmustine), retinoids, imiquimod, and phototherapy (UVB or PUVA). There is no standard initial therapy, and experts differ in their preferred approach. Alternatively, for patients with generalized tumors (e.g., >10 percent body surface area), equally acceptable treatment options are the use of total skin electron beam therapy (TSEBT) and systemic therapies. TSEBT often provides a complete response (CR), albeit temporary in most cases, while systemic agents generally provide partial responses but can be given in a maintenance fashion. A choice among these treatments is made based on patient preference and clinician experience. Despite decades of experience in the treatment of SS and

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- MF, well-designed, prospective, controlled clinical studies comparing the efficacy of various therapies are lacking.
- V. NCCN guideline for the treatment of recurrent or advanced CTCL (MF and SS) includes vorinostat (Zolinza) as one of the preferred regimens (category 2A recommendation). Systemic therapies in this space generally involve use of single agents. Multiagent chemotherapy regimens are reserved for patients, who have progressed after multiple agents in the preferred regimens (e.g. bexarotene, brentuximab, interferons, methotrexate, mogamulizumab, romidepsin). Participants in the clinical trials for vorinostat (Zolinza) did not have a history of prior treatment with an HDAC inhibitor. Efficacy and safety of vorinostat (Zolinza) after progression on another HDAC inhibitor (e.g. romidepsin) has not been studied. Additionally, Safety of combining TSEBT and phototherapy with vorinostat (Zolinza) is unknown. NCCN guideline for primary T-Cell lymphoma recommend against such combination regimen.
 - VI. In an open-label, single-arm, multicenter, nonrandomized clinical trial (N= 74), patients (median age 61 years) with advanced refractory CTCL were treated with vorinostat (400 mg daily). An objective clinical response of 30% was reported with median duration of response 4 weeks. The majority of patients (82.4%) had stage IIB and higher CTCL and had previously failed a median of 3 prior systemic therapies (range, 1 to 12). The primary efficacy endpoint was measured as either a complete clinical response or partial response (i.e. $\geq 50\%$ decrease in a modified severity weighted assessment tool (SWAT) score from baseline) ORR was 29.7% (n= 22) (95% CI; 19.7, 41.5) The median times to response for the overall population and individuals with stage IIB and higher CTCL was 55 days and 56 days (range, 28 to 171 days), respectively. The median time to tumor progression (50% increase in the SWAT score from the nadir) was 202 days. Response to previous systemic therapy was not a response predictor to vorinostat.
 - VII. In a phase 2, open-label, single-center, nonrandomized trial (n=33, median age 67 years), vorinostat exhibited treatment response among previously-treated patients with relapsed or refractory CTCL. The majority (85%) patients had stage IIB and higher CTCL, and were refractory to, or intolerant to, prior systemic therapies (median, 5; range, 1 to 15). Patients were assigned to one of the 3 groups: group 1: vorinostat 400 mg daily (n=13); group 2: vorinostat 300 mg twice daily for 3 days with 4 days rest (n=11) and group 3: vorinostat 300 mg twice daily for 14 days with 7 days rest, followed by 200 mg twice daily (n=9). Oral retinoids, vitamin A or alternative medicines were not allowed. Physician's global assessment (PGA) scores were used for assessing improvement/ partial response. Based on the intent-to-treat analysis, the ORR were 31%, 9%, and 33% in groups 1, 2, and 3, respectively. The ORR was 24.2% (n= 8) in the overall population, 25% (n= 7) in individuals with stage IIB or higher disease, and 36.4% (n= 4) in patients with Sezary syndrome.
 - VIII. During clinical trials, participants receiving vorinostat (Zolinza) reported significant adverse reactions and drug toxicity events. Fatigue (73%), thrombocytopenia (54%), diarrhea (49%), nausea (49%), and dysgeusia (46%) were the most common adverse drug reactions leading to dose reductions. Overall, 19% participants discontinued treatment due to adverse reactions. Vorinostat has been included in the Institute for Safe Medication Practices (ISMP) list of drug classes, which have a heightened risk of causing significant patient harm when used in error.

Investigational or Not Medically Necessary Uses

- I. There is insufficient evidence to support the use of vorinostat (Zolinza) for conditions other than cutaneous T-cell lymphoma.
 - A. Malignant pleural mesothelioma: Vorinostat (Zolinza) showed some evidence of efficacy in an initial phase I study. However, extensive evaluation did not confirm a clinically meaningful benefit from this approach. In a phase III trial, 661 previously treated patients were randomly assigned to either vorinostat or placebo. Progression free survival (PFS) was prolonged with vorinostat (median, 6.3 weeks versus 6.1 weeks; hazard ratio [HR] 0.75, 95% CI 0.63-0.88). However, this increase was not clinically significant. Also, the difference in overall survival was not significant (median, 30.7 weeks versus 27.1 weeks; HR 0.98, 95% CI 0.83-1.17).

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Policy Implementation/Update:

Action and Summary of Changes	Date
Criteria transitioned to policy format. Added criteria noting combination of Zolinza with other oncolytic drugs and skin-directed therapies not allowed; Added requirement of member not having progressed on HDAC inhibitors; updated detailed requirements for failure of two systemic regimens with drug classes (based on NCCN guideline and clinical data); Added investigational uses and supporting evidence section to support the intent of this PA policy	01/2021
Criteria reviews and updates	09/2012; 12/2012; 01/2013
Criteria created	03/2012

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP248

Description

Vosoritide (Voxzogo) is a daily subcutaneously administered C type natriuretic peptide.

Length of Authorization

- Initial: Six months
- Renewal: Six months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
vosoritide (Voxzogo)	0.4 mg vials	To increase linear growth, in pediatric patients with achondroplasia	30 vials/30 days
	0.56 mg vials		
	1.2 mg vials		

Initial Evaluation

- I. **Vosoritide (Voxzogo)** may be considered medically necessary when the following criteria are met:
 - A. Member is one month or older; **AND**
 - B. Member weighs 3kg or more; **AND**
 - C. Medication is prescribed by, or in consultation with, a pediatric specialist in one of the following areas: neurology, orthopedic surgery, endocrinology, genetics; **AND**
 - D. A diagnosis of **achondroplasia**; **AND**
 1. Provider attestation to the following:
 - i. Genetic testing has been done to confirm diagnosis; **AND**
 - ii. Epiphyses are open, as confirmed by radiographic imaging completed in the previous three months; **AND**
 - iii. Member will not receive growth hormone treatment (e.g., Genotropin, Norditropin) concurrently with vosoritide (Voxzogo); **AND**
 - iv. Limb lengthening surgery has not been performed in the past 18 months; **AND**
 - v. At the time of vosoritide (Voxzogo) request, limb lengthening surgery is not planned to occur prior to closure of the epiphyses; **AND**
- II. Vosoritide (Voxzogo) is considered investigational when used for all other conditions, including but not limited to:
 - A. Forms of dwarfism other than achondroplasia
 - B. For growth in patients with achondroplasia when epiphyses are closed
 - C. Combination therapy with growth hormone treatment or limb-lengthening surgery

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Provider attestation to the following:
 - A. If the member is 12 years of age or older or if epiphyses could be closed (e.g., precocious puberty, no height gained in previous few months): radiographic imaging on long bones has been completed within the past year to confirm epiphyses remain open (i.e., potential for growth still remains); **AND**
 - B. Member will not receive growth hormone treatment (e.g., Genotropin, Norditropin) concurrently with vosoritide (Voxzogo); **AND**
 - C. Limb lengthening surgery has not been performed in the past 18 months; **AND**
 - D. At the time of vosoritide (Voxzogo) request, limb lengthening surgery is not planned to occur prior to closure of the epiphyses; **AND**
- IV. Provider attestation that the most recent annualized growth velocity (AGV) is greater than the baseline AGV

Supporting Evidence

- I. Vosoritide (Voxzogo), is FDA-approved to increase linear growth in pediatric patients with achondroplasia. It is a daily subcutaneous (SC) injection with dose based on patient body weight. In 2023, it was evaluated for safety and efficacy in patients at least one month of age and older, receiving FDA-approval in this age group. This expands the original label of those five and older with achondroplasia.
- II. Achondroplasia is a condition of disproportionate short stature and affects 1:20,000 births. Gene mutations permanently activate the FGFR3 receptors, inhibit chondrocyte proliferation, and impair bone formation. Vosoritide (Voxzogo) is the first pharmacotherapy FDA-approved for this condition. There are no formal U.S. guidelines for the treatment of achondroplasia; however, management is highly specialized. Thus, a specialist prescriber is required.
- III. Achondroplasia is caused by variants in the FGFR3 gene, and is recognized on genetic testing. Vosoritide (Voxzogo) targets the root cause of the condition, and safety and efficacy in other causes of forms of dwarfism are unknown, and is not expected to increase linear growth in other conditions. To rule out other causes or forms of dwarfism, genetic testing is required.
- IV. Outside of lifestyle management (e.g., adaptation of home and school environments) and adjunctive care (e.g., treatment for sleep apnea), limb lengthening surgery may be considered. Surgery may be performed at any time, prior to or after epiphyses (i.e., growth plate) close. Evidence suggests there is greater success with surgery after epiphyses have closed. Therapy has not been evaluated for safety and efficacy in those that have received limb lengthening surgery within the past 18 months, or in conjunction with limb lengthening surgery. If surgery has been completed, vosoritide (Voxzogo) therapy should not be used within an 18-month window of surgery, to realize the benefits of surgical intervention. Furthermore, safety and efficacy of this therapy in conjunction with or to prepare for surgery has not been evaluated. Additionally, it is unknown if use of vosoritide (Voxzogo) will have additive effects if used prior to surgery; thus, if surgery is planned or expected prior to final height being reached (e.g., closed epiphyses), therapy should be discontinued.

- V. Vosoritide (Voxzogo) is not expected to provide further linear growth after epiphyses close. FDA and manufacturer guidance indicate that if epiphyses close, therapy should be discontinued at this time. Additionally, therapy should not be initiated in patients that have epiphysial closure. Routine imaging should be completed to evaluate medical necessity for therapy, and is required for initiation of therapy, as well as for renewal evaluation in patients of 12 years of age and older given the greater potential of epiphysial closure at in adolescence.
- VI. Growth hormone therapy is controversial in patients with achondroplasia. It is not commonly used in the U.S. as evidence suggests this may exacerbate the disproportionate stature; however, evidence is conflicting. Dual therapy has not been evaluated for safety or efficacy; thus, concurrent use is not allowed.
- VII. Vosoritide (Voxzogo) was evaluated in a Phase 3, randomized, blinded, placebo-controlled trial in 121 patients that were at least five years of age. Baseline AGV was around 4 cm/year for all patients. The primary outcome was an increase in annualized growth velocity (AGV) over baseline, which was statistically significant for vosoritide (Voxzogo) over placebo with an increase in AGV of 1.71 cm/year, compared to 0.13 cm/year. Therapy was also evaluated in a one-year, open-label extension trial where patients could continue therapy, and those originally randomized to placebo were switched to vosoritide (Voxzogo). The crossover group achieved an AGV of 1.62 cm/year, further supporting the pivotal trial results that therapy may influence an increase a 1.5-1.6 cm increase in AGV. Vosoritide (Voxzogo) has not yet shown to improve other disease manifestations, function, QoL, or reduction surgical intervention need. Vosoritide (Voxzogo) was granted Priority Review, Accelerated Approval, and Orphan Drug Designations. There will be a long-term, open-label trial to evaluate the drug's impact on final height. To assess if there has been an increase in AGV for patients on vosoritide (Voxzogo) therapy, a recently measured baseline AGV is required prior to initiation, as well as upon each renewal to determine if there is a continued treatment effect. In absence of continued treatment effect, continuation of therapy is not warranted at this time.
- VIII. In 2023, vosoritide (Voxzogo) received approval by the FDA for an age expansion into those one month of age and older. This approval was based on a 52-week, phase 2, double-blind, placebo-controlled trial (Study 111-206) which evaluated the safety and efficacy in children with achondroplasia 0-60 months of age. There was a total of 75 patients, 43 received vosoritide and 32 placebo; patients were enrolled over three cohorts which assessed two different doses. Primary endpoints assessed the safety and tolerability, as well as the change from baseline in length/height Z-score. The change from baseline in AGV was measured as a secondary endpoint. Vosoritide (Voxzogo) was well tolerated with a safety profile consistent with those patients over five years of age. All patients had one adverse event with the most common being injection pain/pain/redness. Over all patients in the 52-week period, there was an improvement of over 0.3 standard deviations (95% CI 0.07, 0.54) in height Z-score with vosoritide (n=43) versus placebo (n=32). This change was consistent with those children over five in the pivotal trial and across the three cohorts. Additionally, there was an increase in AGV of 0.92cm/year (95% CI 0.24, 1.59) with vosoritide compared to placebo. Vosoritide (Voxzogo) is weight based; thus, a recent weight from growing pediatric patients is required for initial and renewal coverage considerations for appropriate dose calculation. There is no data or experience in treating those under 3 kilograms.

Investigational or Not Medically Necessary Uses

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- I. Vosoritide (Voxzogo) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Forms of dwarfism other than achondroplasia. Vosoritide (Voxzogo) counteracts the genetic mutation that causes achondroplasia. In addition to lack of evidence for safety and efficacy, there is no expectation that therapy would be effective for other conditions, including other forms of dwarfism or short stature (e.g., growth hormone deficiency, Turner syndrome).
 - B. For growth in patients with achondroplasia when epiphyses are closed
 - C. Combination therapy with growth hormone treatment or limb-lengthening surgery

References

1. Voxzogo [Prescribing Information]. BioMarin Pharmaceutical Inc., Novato, CA. December 2021. Revised October 2023.
2. Savarirayan R, Tofts L, Irving M, et al. Once-daily, subcutaneous vosoritide therapy in children with achondroplasia: a randomised, double-blind, phase 3, placebo-controlled, multicentre trial. *Lancet*. 2020;396(10252):684-692.
3. Randel A. Aap guidelines on health supervision of patients with achondroplasia. *AFP*. 2006;73(6):1112.
4. Coste J, et al. Height and health-related quality of life: a nationwide population study. *J Clin Endocrinol Metab*. 2012;97(9):3231-3239.
5. Vosoritide product dossier. BioMarin. November 30, 2023.

Policy Implementation/Update:

Action and Summary of Changes	Date
Update to the policy and supporting evidence to include age expansion in those one month and older; removed requirement of documentation of current AGV and weight on initial and renewal	02/2024
Policy created	02/2022

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP319

Description

Solriamfetol (Sunosi) is a dopamine and norepinephrine reuptake inhibitor (DNRI).

Pitolisant (Wakix) is a histamine-3 receptor antagonist/reverse agonist.

Sodium oxybate (Xyrem, Lumryz) and calcium, magnesium, potassium, sodium oxybates (Xywav) are orally administered metabolites of the neurotransmitter GABA that act as central nervous system depressants with an unknown mechanism of action.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
solriamfetol (Sunosi)	75 mg tablets	Excessive sleepiness associated with either OSA or narcolepsy in adults	60 tablets/30 days
	150 mg tablets		30 tablets/30 days
pitolisant (Wakix)	4.45 mg tablets	Excessive daytime sleepiness (EDS) or cataplexy in adult patients with narcolepsy	60 tablets/30 days
	17.8 mg tablets	Excessive daytime sleepiness (EDS) in pediatric patients 6 years of age and older with narcolepsy	60 tablets/30 days
generic sodium oxybate	500 mg/mL solution	Narcolepsy with cataplexy or excessive daytime sleepiness in patients greater than 7 years of age Idiopathic hypersomnia in adults	540 mL/30 days
sodium oxybate (Xyrem)			
calcium, magnesium, potassium, sodium oxybates (Xywav)			
sodium oxybate oral powder for suspension (Lumryz)	4.5 g packet	Narcolepsy with cataplexy or excessive daytime sleepiness in patients 7 years of age and older	135 grams/30 days
	6 g packet		180 grams/ 30 days
	7.5 g packet		225 grams/ 30 days
	9 g packet		270 grams/ 30 days
sodium oxybate oral powder for suspension (Lumryz Starter Pack)	Starter Pack	Idiopathic hypersomnia in adults	28 packets/28 days

Initial Evaluation

- I. **Solriamfetol (Sunosi), pitolisant (Wakix), generic sodium oxybate, sodium oxybate (Xyrem), sodium oxybate ER (Lumryz), or calcium, magnesium, potassium, sodium oxybate (Xywav)** may be considered medically necessary when the following criteria below are met:
 - A. Medication is prescribed by, or in consultation with, a sleep specialist, psychiatrist, or neurologist; **AND**

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- B. If request is for generic sodium oxybate, sodium oxybate (Xyrem), sodium oxybate ER (Lumryz), or calcium, magnesium, potassium, sodium oxybate (Xywav):
 1. Medication will not be used in combination with sedative hypnotic agents (e.g. benzodiazepines, barbiturates, zolpidem tartrate); **AND**
 2. Provider attestation the member does not have a succinic semialdehyde dehydrogenase deficiency; **AND**
 3. Provider attestation the member does not have a history of substance abuse; **AND**
 4. The request is for brand Xyrem; **AND**
 - i. Documentation of intolerance or contraindication to generic sodium oxybate; **AND**
- C. A diagnosis of one of the following:
 1. **Type 1 Narcolepsy (narcolepsy with cataplexy); AND**
 - i. Confirmation of cataplexy defined as episodes of sudden loss of muscle tone; **AND**
 - ii. Documented impairment/limitation of activities of daily living (e.g. missing school/work, household chores, driving); **AND**
 - iii. The request is for pitolisant (Wakix); **AND**
 - a. Member is six years of age or older; **OR**
 - iv. The request is for generic sodium oxybate, sodium oxybate (Xyrem), sodium oxybate ER (Lumryz), or calcium, magnesium, potassium, sodium oxybate (Xywav); **AND**
 - a. Member is seven years of age or older; **AND**
 - b. Documentation that treatment with pitolisant (Wakix) has been ineffective, contraindicated or not tolerated; **OR**
 2. **Type 2 Narcolepsy (narcolepsy without cataplexy); AND**
 - i. Confirmation of diagnosis with a sleep study (including polysomnography and multiple sleep latency test); **AND**
 - ii. Documented impairment/limitation of activities of daily living (e.g. missing school/work, household chores, driving); **AND**
 - iii. Treatment with the following has been ineffective, contraindicated, or not tolerated:
 - a. A stimulant (e.g., methylphenidate, amphetamine salts, or dextroamphetamine, etc.); **AND**
 - b. Modafinil (Provigil) or armodafinil (Nuvigil); **AND**
 - iv. The request is for solriamfetol (Sunosi); **AND**
 - a. Member is 18 years of age and older; **OR**
 - v. The request is for pitolisant (Wakix); **AND**
 - a. Member is six years of age or older; **AND**
 - b. Treatment with solriamfetol (Sunosi) has been ineffective, contraindicated, or not tolerated for those 18 years of age and older; **OR**
 - vi. The request is for generic sodium oxybate, sodium oxybate (Xyrem), sodium oxybate ER (Lumryz), or calcium, magnesium, potassium, sodium oxybate (Xywav); **AND**

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- a. Member is seven years of age or older; **AND**
 - b. Treatment with solriamfetol (Sunosi) has been ineffective, contraindicated, or not tolerated for those 18 years of age and older; **AND**
 - c. Treatment with pitolisant (Wakix) has been ineffective, contraindicated, or not tolerated; **OR**
 - 3. **Excessive Daytime Sleepiness associated with Obstructive Sleep Apnea (OSA); AND**
 - i. The request is for solriamfetol (Sunosi); **AND**
 - ii. Member is 18 years of age and older; **AND**
 - iii. The member has current or prior use of a primary OSA therapy (e.g., CPAP, mandibular advancement device or surgical intervention); **AND**
 - iv. Treatment with modafinil (Provigil) or armodafinil (Nuvigil) has been ineffective, contraindicated, or not tolerated; **OR**
 - 4. **Idiopathic hypersomnia; AND**
 - i. Member is 18 years of age or older; **AND**
 - ii. The request is for generic sodium oxybate, sodium oxybate (Xyrem), sodium oxybate ER (Lumryz), or calcium, magnesium, potassium, sodium oxybate (Xywav); **AND**
 - iii. Provider attestation that hypersomnia is not better explained by medical or neurological disorder, mental disorder, medication use, or substance use disorder; **AND**
 - iv. Provider attestation that diagnosis has been confirmed via the following:
 - a. Polysomnography; **AND**
 - b. Multiple sleep latency test; **AND**
 - v. Treatment with ALL of the following has been ineffective, contraindicated, or not tolerated:
 - a. Modafinil (Provigil) or armodafinil (Nuvigil); **AND**
 - b. A stimulant (e.g., methylphenidate, amphetamine salts, or dextroamphetamine, etc.)
- II. Sodium oxybate (Xyrem, Lumryz) and calcium, magnesium, potassium, sodium oxybates (Xywav), solriamfetol (Sunosi), and pitolisant (Wakix) are considered investigational when used for all other conditions, including but not limited to:
- 1. Excessive sleepiness associated with Parkinson's Disease or glioblastoma
 - 2. Shift work sleep disorder (SWSD)
 - 3. Attention-deficit/hyperactivity disorder (ADHD)
 - 4. Fatigue not related to narcolepsy or OSA
 - 5. Fibromyalgia
 - 6. Insomnia
- A. Solriamfetol (Sunosi)
- 1. Major depressive disorder
 - 2. Steinert myotonic dystrophy syndrome
 - 3. Type 1 narcolepsy (narcolepsy with cataplexy)

B. Pitolisant (Wakix)

1. Excessive daytime sleepiness associated with obstructive sleep apnea
2. Idiopathic hypersomnia
3. Refractory restless legs syndrome
4. Autism spectrum disorders
5. Prader-Willi Syndrome

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Member has exhibited improvement or stability of disease symptoms [e.g., reduction in cataplexy attacks, improvement in ability to complete activities of daily living, improvement in ability to stay awake]; **AND**
- IV. If request is for generic sodium oxybate, sodium oxybate (Xyrem), sodium oxybate ER (Lumryz), or calcium, magnesium, potassium, sodium oxybate (Xywav) medication will not be used in combination with sedative hypnotic agents (e.g., benzodiazepines, barbiturates, zolpidem tartrate, etc.)

Supporting Evidence

- I. Narcolepsy is a chronic neurological disorder that affects the brain's ability to control sleep-wake cycles. Narcolepsy can greatly affect daily activities. All individuals with narcolepsy have excessive daytime sleepiness (EDS), and it is often the most obvious symptom. Excessive daytime sleepiness is characterized by persistent sleepiness, regardless of how much sleep an individual gets at night. Similarly, many patients with obstructive sleep apnea (OSA) and idiopathic hypersomnia (IH) experience excessive daytime sleepiness, which can negatively affect daily functioning, cognition, mood, and other aspects of well-being. Given the complexities of diagnosis and treatment of these conditions, supervision of treatment by a sleep specialist, psychiatrist, or neurologist is required.
- II. Sodium oxybate (Xyrem, Lumryz) and calcium, magnesium, potassium, sodium oxybates (Xywav) are a part of REMS programs which only allow certified prescribers and pharmacies to dispense these medications. Prescribers must screen each patient for a history of alcohol or substance abuse, sleep-related breathing disorders, compromised respiratory function, depression or suicidality, and concomitant use of sedative hypnotics, other CNS depressants, or other potentially interacting agents.
- III. Sodium oxybate (Xyrem, Lumryz) and calcium, magnesium, potassium, sodium oxybates (Xywav) are contraindicated in patients taking sedative hypnotic agents (e.g., benzodiazepines, barbiturates, zolpidem tartrate), and in patients with a succinic semialdehyde dehydrogenase deficiency. Sodium oxybate (Xyrem, Lumryz) and calcium, magnesium, potassium, sodium oxybates (Xywav) have serious side effects such as, central nervous system depression, abuse and misuse, respiratory depression and sleep-disordered breathing, depression and suicidality,

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parasomnias, other psychiatric reactions (e.g., anxiety, hallucinations, psychosis), and elevates salt content (use with caution in patients that have heart failure, hypertension, or renal impairment).

- IV. Outside of salt content, there is no clinical difference between sodium oxybate (Xyrem) and calcium, magnesium, potassium, sodium oxybates (Xywav). Both agents are oral solutions taken twice nightly. Sodium oxybate (Lumryz) is an extended-release oral powder for suspension that is taken once nightly and contains the same active ingredient as sodium oxybate (Xyrem). Although falls while receiving oxybate treatment have been reported in clinical trials and post-marketing reports, no basis exists to attribute an increased risk of falls to a second nightly dose. Furthermore, each product's drug information label discourages getting out of bed after any oxybate dosing due to sedation. Pitolisant (Wakix) is FDA-approved for the treatment of cataplexy or excessive daytime sleepiness in pediatric patients and adults with narcolepsy. Solriamfetol (Sunosi) is FDA-approved for the treatment of excessive daytime sleepiness associated with OSA and narcolepsy in adults.
- V. There are no direct head-to-head studies comparing pitolisant (Wakix), solriamfetol (Sunosi), sodium oxybate (Xyrem, Lumryz), and calcium, magnesium, potassium, sodium oxybates (Xywav) to establish superior safety or efficacy of one product over the other. However, there are substantial cost differences between products despite not having any evidence of improved clinical efficacy or safety.

Type 1 Narcolepsy (narcolepsy with cataplexy) and Type 2 Narcolepsy (narcolepsy without cataplexy)

- VI. All individuals with narcolepsy have EDS, and it is often the most obvious symptom of the disease. While all individuals with narcolepsy will have EDS, cataplexic attacks may or not be characteristic of the patient's disease. Cataplexy is defined as the sudden loss of muscle tone while a person is awake leads to weakness and a loss of voluntary muscle control. It is often triggered by sudden, strong emotions such as laughter, fear, anger, stress, or excitement. The symptoms of cataplexy may appear weeks or even years after the onset of EDS. Some people may only have one or two attacks in a lifetime, while others may experience many attacks a day. Attacks may be mild and involve only a momentary sense of minor weakness in a limited number of muscles, such as a slight drooping of the eyelids. The most severe attacks result in a total body collapse during which individuals are unable to move, speak, or keep their eyes open. But even during the most severe episodes, people remain fully conscious, a characteristic that distinguishes cataplexy from fainting or seizure disorders. The loss of muscle tone during cataplexy resembles paralysis of muscle activity that naturally occurs during REM sleep. Episodes last a few minutes at most and resolve almost instantly on their own. The presence or absence of cataplexy helps distinguish between type 1 and type 2 narcolepsy. Type 1 narcolepsy (previously known as narcolepsy with cataplexy) is diagnosed based on the individual either having low levels hypocretin or reporting cataplexy and having excessive daytime sleepiness via polysomnography or multiple sleep latency test. Type 2 narcolepsy (previously known as narcolepsy without cataplexy) includes patients with EDS that usually do not have muscle weakness triggered by emotions. They frequently have less severe symptoms and have normal levels of the brain hormone hypocretin. Type 2 narcolepsy is also diagnosed with polysomnography or multiple sleep latency test per ICSD-3-TR diagnostic criteria.
- VII. The American Academy of Sleep Medicine clinical practice guideline (2021) establishes clinical practice recommendations for treatment of central disorders of hypersomnolence. In adults with narcolepsy, there are strong recommendations for modafinil, pitolisant (Wakix), sodium oxybate, and solriamfetol (Sunosi) for the treatment of narcolepsy in adults. There are

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conditional recommendations for armodafinil, dextroamphetamine, and methylphenidate for the treatment of narcolepsy in adults. However, only pitolisant (Wakix), sodium oxybate, and dextroamphetamine have shown clinically significant improvements in cataplexy. For pediatric patients with narcolepsy, the guidelines place conditional recommendations for modafinil and sodium oxybate. Similar to adult populations, only pitolisant (Wakix) have critical outcomes showing clinically significant improvements in the treatment of cataplexy in children. Guidelines have not been updated since the FDA approved pitolisant (Wakix) for the treatment of treatment of excessive daytime sleepiness (EDS) in pediatric patients 6 years of age and older with narcolepsy.

VIII. A joint European guideline from the European Academy of Neurology (EAN), the European Sleep Research Society (ESRS) and the European Narcolepsy Network (EU-NN) (2021) establishes clinical practice recommendations for the management of narcolepsy in both adults and children. EAN/ESRS/EU-NN guidelines recommend therapies in a sequential manner dependent on primary symptomatology (EDS unique, EDS with cataplexy, and EDX with cataplexy and disturbed nocturnal sleep). Guidelines acknowledge that given a lack of head-to-head studies, comparisons of efficacy between different stimulants/wake-promoting drugs are difficult. The main pharmacotherapy recommendations can be summarized as follows:

- Excessive daytime sleepiness (EDS) in adults – modafinil, pitolisant (Wakix), sodium oxybate (SXB), solriamfetol (Sunosi) (all strong); methylphenidate, amphetamine derivatives (both weak)
- EDS with cataplexy in adults – SXB, venlafaxine, clomipramine (all strong) and pitolisant (Wakix) (weak)
- EDS in children– SXB (strong), modafinil, methylphenidate, pitolisant (Wakix), amphetamine derivatives (all weak)
- EDS with cataplexy in children – SXB (strong), antidepressants (weak).

IX. Pitolisant (Wakix) is FDA-approved for the treatment of excessive daytime sleepiness in patients six years of age or older with narcolepsy. Pitolisant (Wakix) was studied in adults in three randomized controlled trials, and one open-label, single-arm, long term safety & efficacy trial. HARMONY I and I bis included modafinil as an active comparator to pitolisant (Wakix). In pediatric patients six years of age or older with narcolepsy, pitolisant (Wakix) was studied in one multicenter, randomized, double-blinded, placebo-controlled study (Study 4).

- HARMONY I (n = 95): The primary efficacy outcome was the change in the Epworth Sleepiness Scale (ESS) score after eight weeks. Pitolisant (Wakix) 35.6 mg demonstrated a statistically greater reduction in the ESS score compared to placebo (change of -3.1 points [-5.73, -0.46]). When compared to modafinil, pitolisant (Wakix) failed to demonstrate non-inferiority for changes in ESS score. The ESS score has been commonly used in standard practice and was originally validated through a study in 1991.
- HARMONY I bis (n = 165): The primary efficacy outcome was the change in the ESS score and compared pitolisant (Wakix) 17.4 mg vs. placebo. Pitolisant (Wakix) demonstrated statistically significant reduction in the ESS score compared to placebo (change of -2.12 points [-4.10, -0.14]). When compared to modafinil, pitolisant (Wakix) failed to demonstrate non-inferiority for changes in ESS score.
- HARMONY CTP (n = 106): The primary efficacy outcome was the change in the average number of cataplexy attacks per week as documented by patient diaries.

The cataplexy ratio rate was 0.51 (0.44-0.60, $p < 0.0001$) for pitolisant (Wakix) compared to placebo.

- HARMONY III (n = 102): Efficacy was a secondary endpoint and was measured by the change in the ESS score from baseline to one year. The mean decrease in ESS scores was -4.6 ± 0.59 (-5.82, -3.44).
- Study 4 (n=110): The primary efficacy outcome was the change in Ullanlinna Narcolepsy Scale (UNS) total score though the FDA approved on the bases of change in excessive daytime sleepiness as measured by the Pediatric Daytime Sleepiness Scale (PDSS). Pitolisant (Wakix) demonstrated statistically significantly greater improvement on the least square mean change from baseline to the end of treatment in final PDSS total score compared to placebo, of -3.41 points (95% CI: -5.52, -1.31).
- The use of pitolisant (Wakix) in the treatment of narcolepsy with cataplexy was established in HARMONY CTP with supporting evidence in HARMONY I. Primary outcomes of HARMONY CTP evaluated weekly rate of cataplexy (WRC) while HARMONY I, Daily Rate of Cataplexy (DRC) was evaluated as a secondary endpoint to support the use in cataplexy. Secondary outcomes of DRC in HARMONY I showed a significant improvement DRC.

- X. Solriamfetol (Sunosi) is FDA-approved for the treatment of adult patients with excessive daytime sleepiness associated with narcolepsy. The efficacy and safety of solriamfetol (Sunosi) was established in a Phase 3, multi-center, double-blind, placebo-controlled, randomized trial which included patients with either type I or type II narcolepsy (n=239). Compared to the placebo group (n= 114), patients randomized to 150 mg solriamfetol (Sunosi) (n=116) showed statistically significant improvements on the MWT (treatment effect difference: 7.7 minutes) and on the ESS (treatment effect difference: 3.8 points). Change in the mean and median weekly number of cataplexy attacks was an exploratory endpoint among the subgroup of patients who reported the presence of cataplexy. These patients completed a cataplexy frequency diary to record the number of cataplexy attacks that they had each day, beginning after discontinuation of narcolepsy medication and through week 12. There was no clear effect of solriamfetol (Sunosi) on the number of cataplexy attacks per week among patients with cataplexy.
- XI. For the treatment of narcolepsy with cataplexy, sodium oxybate (Xyrem) was evaluated in two randomized, double-blind, placebo-controlled, multicenter, parallel-group trials with a total of 191 patients. Over 80% of patients in these trials were on stimulants as background therapy. The primary efficacy endpoint was the median change from baseline in cataplexy attacks. The baseline number of cataplexy attacks was 20 and 23 for the placebo group and Xyrem 9 g group, respectively. Trial one had a reduction of 16 attacks per week in the 9g treatment group and 4 attacks per week in the placebo group ($p=0.0016$). Trial two was a randomized withdrawal trial, and the placebo group had 21 attacks within two weeks, while the sodium oxybate (Xyrem) group had zero attacks within two weeks ($p < 0.001$).
- XII. For the treatment of narcolepsy with excessive daytime sleepiness, sodium oxybate (Xyrem) was evaluated in two randomized, double-blind, placebo-controlled trials with a total of 450 patients. The primary efficacy endpoint for trial three was the change from baseline in the Epworth Sleepiness Scale (EPSS). Sodium oxybate (Xyrem) had a -2 and -5 median change from baseline at week 8 for the 6g and 9g treatment groups, and both groups had statistically greater

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reductions than the placebo group ($p < 0.001$). The primary efficacy endpoint for trial four was the change from baseline in the Maintenance of Wakefulness Test (MWT). Sodium oxybate (Xyrem) had a mean change from baseline of 0.6 compared to -2.7 for placebo at week 8 ($p < 0.001$).

- XIII. For the treatment of narcolepsy with cataplexy and excessive daytime sleepiness in pediatrics, sodium oxybate (Xyrem) was evaluated in one double-blind, placebo-controlled, randomized-withdrawal trial with 106 pediatric patients. Patients included in this study were seven to 16 years of age. The primary efficacy endpoints were the change in the frequency of cataplexy attacks and EPSS. The median change from baseline in the number of cataplexy attacks per week was 0.3 for sodium oxybate (Xyrem) compared to 12.7 for placebo ($p < 0.0001$). The median change in the EPSS was zero for sodium oxybate (Xyrem) and three for placebo ($p = 0.0004$).
- XV. Sodium oxybate (Lumryz) is FDA-approved for treatment of narcolepsy with cataplexy and excessive daytime sleepiness in pediatric patients seven years of age and older as well as adults. Safety and efficacy in adult populations was evaluated in the REST-ON trial, a double-blind, randomized, placebo-controlled trial that evaluated once nightly administration of sodium oxybate (Lumryz) in 212 patients with narcolepsy, 16 years of age or older. Patients were randomized 1:1 to receive sodium oxybate (Lumryz) or placebo. The study consisted of 13-weeks of treatment of escalating doses (g/night) of sodium oxybate (Lumryz) at 4.5 g week one, 6 g weeks two-three, 7.5 g weeks four-eight, and 9 g weeks nine-thirteen. The three co-primary endpoints were the maintenance of wakefulness test (MWT), clinical global Impression-improvement (CGI-I), and mean change in weekly cataplexy attacks. A statistically significant improvement was seen on the MWT, CGI-I, and mean weekly cataplexy attacks, for the 6 g (Week 3), 7.5 g (Week 8), and 9 g (Week 13) dose of sodium oxybate (Lumryz) compared to the placebo group ($p < 0.001$).
- XVI. The effectiveness of sodium oxybate (Lumryz) for cataplexy and excessive daytime sleepiness (EDS) in pediatric narcolepsy is based upon a clinical study in patients treated with immediate-release sodium oxybate (Xyrem).

Excessive Daytime Sleepiness associated with Obstructive Sleep Apnea

- XVI. Obstructive sleep apnea (OSA) is a sleep-related breathing disorder resulting from repetitive collapse of the upper airway, which causes intermittent episodic hypoxia and impaired ventilation during sleep. OSA is diagnosed based on the presence of positive polysomnography (PSG) or home sleep apnea test findings of predominantly obstructive respiratory events (e.g., apneas, hypopneas, or respiratory effort-related arousals).
- XVII. Per AASM guidelines for the Evaluation, Management, and Long-Term Care of Obstructive Sleep Apnea in Adults state positive airway pressure (PAP) is the treatment of choice for mild, moderate, and severe OSA and should be offered as an option to all patients. Additionally, custom made oral appliances (OA), such as mandibular repositioning appliances, may improve upper airway patency during sleep by enlarging the upper airway and/or by decreasing upper airway collapsibility. Although not as efficacious as CPAP, OAs are indicated for use in patients with mild to moderate OSA who prefer OAs to CPAP, or who do not respond to CPAP, are not appropriate candidates for CPAP, or who fail CPAP or behavioral measures such as weight loss or sleep position change.
- XVIII. EDS can be a prominent symptom of OSA and occurs when sleepiness intrudes into activities of daily living. Although EDS can be reduced with primary OSA treatment, such as continuous

positive airway pressure (CPAP) therapy, a substantial proportion of patients continue to experience EDS despite receiving optimized primary OSA therapy.

- XIX. AASM guidelines recommend use of modafinil for the treatment of residual excessive daytime sleepiness in OSA patients who have sleepiness despite effective PAP treatment who are lacking any other identifiable cause for their sleepiness. Prior to use of modafinil other causes of residual sleepiness should be ruled out including suboptimal objective adherence with PAP, ill-fitting PAP masks, insufficient sleep, poor sleep hygiene, and other sleep disorders (e.g., narcolepsy, restless leg syndrome, depression, etc.).
- XX. The efficacy and safety of solriamfetol (Sunosi) for the treatment of adults (18 and older) with EDS and OSA was demonstrated in a 12-week, multi-center, randomized, double-blind, placebo-controlled trial of 476 patients. In clinical trials, patients with OSA were required to be stable for greater than one month on primary OSA therapy (e.g. CPAP, mandibular advancement device, or surgical intervention) prior to use of solriamfetol (Sunosi). Participants were randomized to receive solriamfetol (Sunosi) 37.5 mg, 75 mg, 150 mg, or 300 mg (two times the maximum recommended daily dose). Compared to the placebo group, patients randomized to 37.5 mg, 75 mg, and 150 mg solriamfetol (Sunosi) showed statistically significant improvements on the MWT (treatment effect difference: 4.5 minutes, 8.9 minutes, and 10.7 minutes respectively) and ESS (treatment effect difference: 1.9 points, 1.7 points, and 4.5 points respectively) at Week 12.

Idiopathic Hypersomnia

- XXI. While sodium oxybate (Xyrem, Lumryz) does not carry an FDA approved indication for use in idiopathic hypersomnia (IH), the active moiety is the same as calcium, magnesium, potassium, sodium oxybates (Xywav). The chemical entity found in both of these products is expected to produce similar efficacy and safety for the treatment of IH.
- XXII. The safety profile of calcium, magnesium, potassium, sodium oxybates (Xywav) and sodium oxybate (Xyrem, Lumryz) in pediatric patients for the treatment of IH has not been established.
- XXIII. Idiopathic hypersomnia (IH) is a sleep disorder that presents as chronic excessive daytime sleepiness (EDS) and difficulty waking up from nighttime sleep or daytime naps. Symptomatic patients are unable to maintain wakefulness and alertness during major waking episodes of the day, with sleep occurring unintentionally. Diagnosis of IH is made by objective sleep tests as well as ruling out other sleep disorders, medical or psychiatric disorders, or use of drugs that may be causing EDS. Hypersomnia associated with psychiatric disorders (i.e., atypical depression, bipolar depression, dysthymia, etc.) is a differential diagnosis and commonly overlaps with complaints of excessive daytime sleepiness and may be mistaken for idiopathic hypersomnia if not ruled out. In patients where hypersomnia may be better explained by other sleep disorders, psychiatric disorders, or use of certain medications, use of sodium oxybate (Xyrem) and calcium, magnesium, potassium, sodium (Xywav) is not considered medically necessary, as treatment of hypersomnia in this setting is guided by correcting the underlying cause.
- XXIV. IH is diagnosed through combined evaluation of nocturnal polysomnography and a multiple sleep latency test (MSLT). Polysomnography can exclude causes of excessive daytime sleepiness (i.e., subtle forms of obstructive sleep apnea) while shortened mean sleep latency and the number of sleep-onset rapid eye movement sleep periods (SOREMPs) can distinguish between narcolepsy and IH.

- XXV. Stimulants and alerting agents (i.e., modafinil, armodafinil, methylphenidate, amphetamine salts) for IH are recommended based on experience with these medications in the setting of excessive daytime sleepiness (EDS) associated with narcolepsy. FDA approval of stimulants and alerting agents in related sleep conditions such as narcolepsy, American Academy of Sleep Medicine clinical guideline recommendations, large body of safety data, and proven effects on EDS support the use of stimulants and alerting agents in IH. Additionally, the majority of clinical trial population for calcium, magnesium, potassium, sodium oxybates (Xywav) were on a stimulant/alerting agent at baseline. Given the known safety profile, extensive clinical use, and cost-effectiveness of these therapies, a trial of stimulants and alerting agents is required.
- XXVI. The efficacy and safety of calcium, magnesium, potassium, sodium oxybates (Xywav) was established in a Phase 3, interventional, double-blind, placebo-controlled, randomized withdrawal trial that evaluated the use of calcium, magnesium, potassium, sodium oxybates (Xywav) in adult patients with IH. Participants were a median age of 39 years, 71% female, 81% white and non-Hispanic or Latino. At baseline 2% of patients were taking Xyrem only, 4% were taking Xyrem in addition to another stimulant/alerting agent, 54% were taking a stimulant/alerting agent, and 41% were naïve to therapy. CNS stimulants were allowed to continue throughout the SDP and DB RWP – this occurred in 57% of patients. Baseline Epworth Sleepiness Scale ESS scores were 16 in calcium, magnesium, potassium, sodium oxybates (Xywav) and 17 in the placebo groups. Efficacy was confirmed in the double blind, randomized, 2-week withdrawal period (DB RWP). Primary outcome showed a statistically significant worsening of median ESS in patients on placebo (Δ 5 to 14 points) when compared to those in the calcium, magnesium, potassium, sodium oxybates (Xywav) arm (Δ 6.5 to 7 points) ($p < 0.0001$).
- XXVII. The efficacy and safety of calcium, magnesium, potassium, sodium oxybates (Xywav) was established in a Phase 3, interventional, double-blind, placebo-controlled, randomized withdrawal trial that evaluated the use of calcium, magnesium, potassium, sodium oxybates (Xywav) in adult patients with IH. Participants were a median age of 39 years, 71% female, 81% white and non-Hispanic or Latino. At baseline 2% of patients were taking Xyrem only, 4% were taking Xyrem in addition to another stimulant/alerting agent, 54% were taking a stimulant/alerting agent, and 41% were naïve to therapy. CNS stimulants were allowed to continue throughout the SDP and DB RWP – this occurred in 57% of patients. Baseline Epworth Sleepiness Scale ESS scores were 16 in calcium, magnesium, potassium, sodium oxybates (Xywav) and 17 in the placebo groups. Efficacy was confirmed in the double blind, randomized, 2-week withdrawal period (DB RWP). Primary outcome showed a statistically significant worsening of median ESS in patients on placebo (Δ 5 to 14 points) when compared to those in the calcium, magnesium, potassium, sodium oxybates (Xywav) arm (Δ 6.5 to 7 points) ($p < 0.0001$).

Investigational or Not Medically Necessary Uses

- I. Sodium oxybate (Xyrem, Lumryz) and calcium, magnesium, potassium, sodium oxybates (Xywav), solriamfetol (Sunosi), and pitolisant (Wakix) currently have insufficient evidence supporting efficacy or safety in the following conditions:

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- A. Shift work sleep disorder (SWSD)
 - B. Attention-deficit/hyperactivity disorder (ADHD)
 - C. Fatigue not related to narcolepsy or OSA
 - D. Excessive sleepiness associated with Parkinson's Disease
 - E. Fibromyalgia
 - F. Insomnia
- II. Solriamfetol (Sunosi) is currently being studied in multiple clinical trials; however, evidence is currently limited to proof-of-concept. There is insufficient safety and efficacy information to support use in the following conditions:
- A. Major depressive disorder
 - B. Steinert myotonic dystrophy syndrome
- III. Pitolisant (Wakix) is currently being studied in multiple clinical trials; however, evidence is currently limited to proof-of-concept. There is insufficient safety and efficacy information to support use in the following conditions:
- A. Excessive daytime sleepiness associated with obstructive sleep apnea
 - B. Idiopathic hypersomnia
 - C. Refractory restless legs syndrome
 - D. Autism spectrum disorders
 - E. Prader-Willi Syndrome

Appendix

I. Treatment Table

	Type 1 Narcolepsy (narcolepsy with cataplexy)	Type 2 Narcolepsy (narcolepsy without cataplexy)	EDS w/ OSA	IH
Generic sodium oxybate	X	X*		X†
Xyrem IR oral soln	X	X*		X†
Lumryz ER oral susp	X*	X*		X†
Xywav	X*	X*		X
Wakix	X‡	X‡		
Sunosi		X	X	
* Adult + Pediatric indication (patients ≥7yo)				
‡ Adult + Pediatric indication (patients ≥6yo)				
† Used off label per policy				

- II. Dose conversion for patients switching from twice nightly oxybate to once nightly sodium oxybate (Lumryz)
- a. Switching from immediate-release sodium oxybate solution, patients may be switched to sodium oxybate extended-release at the nearest equivalent dosage in grams per

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Related Policies

Currently there are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
Updates to combine Xyrem, Lumryz, Xywav, Wakix, and Sunosi into one Wakefulness Agents policy. Update to include age expansion of pitolisant (Wakix) for pediatrics 6 years and older and sodium oxybate ER (Lumryz) for pediatric patients 7 years and older. Update supporting evidence to include disease state background and terminology of type 1 or type 2 narcolepsy. Updated to allow initial authorization of 12 months.	04/2025
Removed criteria “Use will not be in combination with sodium oxybate (Xyrem) or calcium, magnesium, potassium, sodium oxybates (Xywav)”	12/2021
Updated policy to include new indication for Wakix use in patients with narcolepsy with cataplexy.	12/2020
Updated policy to require trial and failure of solriamfetol (Sunosi) prior to approval of pitolisant (Wakix) for narcolepsy.	06/2020
Addition of pitolisant (Wakix) information for coverage including: experimental/investigational, coverage for narcolepsy, quantity limits, and evidence base.	09/2019

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New policy for solriamfetol (Sunosi).	08/2019

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP171

Split Fill Management*

Description

Zanubrutinib (Brukinsa) is an orally administered Bruton's Tyrosine Kinase (BTK) inhibitor.

Length of Authorization

- Initial: Six months (first three months split fill)
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
zanubrutinib (Brukinsa)	Mantle cell lymphoma in adults who have received at least one prior therapy	80 mg capsule	120 capsules/30 days
	Relapsed or refractory follicular lymphoma (FL), in combination with obinutuzumab, after two or more lines of systemic therapy		
	Waldenström's macroglobulinemia in adults	160 mg tablets	60 tablets/30 days
	Chronic lymphocytic leukemia or small lymphocytic lymphoma in adults		
	Relapsed or refractory marginal zone lymphoma in adults who have received at least one anti-CD20-based regimen		

Initial Evaluation

- I. **Zanubrutinib (Brukinsa)** may be considered medically necessary when the following criteria below are met:
 - A. Member is 18 years of age or older; **AND**
 - B. Medication is prescribed by, or in consultation with, an oncologist, or hematologist; **AND**
 - C. Member has not previously progressed on a BTK inhibitor [e.g., ibrutinib (Imbruvica), acalabrutinib (Calquence)]; **AND**
 - D. A diagnosis of one of the following:
 1. **Waldenström's Macroglobulinemia (WM); AND**
 - i. Medication will not be used in combination with any other oncolytic medication; **AND**
 - ii. Member has received one prior therapy [e.g., chemotherapy, rituximab (Rituxan)]; **OR**

- iii. Provider attestation that member is not a candidate for standard immunochemotherapy based on documented risk factors or comorbidities; **OR**
 - 2. **Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL); AND**
 - i. Medication will not be used in combination with any other oncolytic medication; **AND**
 - ii. Medication is used in previously untreated CLL/SLL; **AND**
 - a. The member does not have a del17p mutation; **OR**
 - iii. Medication is used in the relapsed/refractory CLL/SLL; **AND**
 - a. Member has received one prior therapy [e.g., chemotherapy, venetoclax (Venclexta), obinutuzumab (Gazyva)]; **OR**
 - 3. **Relapsed/Refractory Follicular Lymphoma (FL); AND**
 - i. Medication will be used in combination with obinutuzumab (Gazyva); **AND**
 - ii. Disease has progressed following two or more FL chemotherapy regimens that have included an anti-CD20 monoclonal antibody (i.e., rituximab) and an alkylating agent (i.e., bendamustine, cyclophosphamide, chlorambucil)
- II. Zanubrutinib (Brukinsa) is considered investigational when used for all other conditions, including but not limited to:
- A. Previously untreated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma in patients with a del17p mutation
 - B. Diffuse Large B-cell Lymphoma (DLBCL)
 - C. Hairy Cell Leukemia (HCL)
 - D. Graft-versus Host Disease (GvHD)
 - E. Marginal Zone Lymphoma (MZL)
 - F. Indolent Non-Hodgkin Lymphoma (iNHL)
 - G. MCL monotherapy
 - H. MCL first-line therapy
 - I. MCL combination therapy
 - J. Richter's Transformation

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. A diagnosis of one of the following:
 - **Waldenström's Macroglobulinemia (WM) or Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL); AND**
 - i. Medication will be used as monotherapy
 - **Relapsed/ Refractory Follicular Lymphoma (FL); AND**
 - i. Medication will be used in combination with obinutuzumab (Gazyva); **AND**
- IV. Member has exhibited improvement or stability of disease symptoms (e.g., no signs of disease progression)

Supporting Evidence

I. WM:

- A. Zanubrutinib (Brukinsa) is FDA-approved for WM based on the non-comparative assessment of DOR from zanubrutinib (Brukinsa) treatment arms and was granted Fast Track and Orphan Drug designation.
- B. Zanubrutinib (Brukinsa) was studied in one Phase 1/2 open-label, dose expansion, single-arm trial of B-cell malignancies (BGB-3111-AU-003) in 77 WM patients and one head-to-head trial against ibrutinib (ASPEN). ASPEN was a Phase 3, randomized, active control, open-label trial which enrolled 137 relapsed/refractory (RR) and 37 treatment naïve WM adult patients. Median number of previously tried therapies included 1 (range: 1-8) and majority (90%) were refractory to anti-CD20 therapies (rituximab, ofatumumab), alkylating agents (88%) (cyclophosphamide, chlorambucil, bendamustine), and glucocorticoids (72%). Treatment naïve patients consisted of those unsuitable for standard immunochemotherapy based on presence of comorbidities or risk factors precluding its use (e.g., age, cardiac, renal, infection comorbidities). Median patient age was 70 years of age. The trial excluded patients with previous exposure to BTK inhibitor therapy and those with WM central nervous system involvement. The primary endpoint of proportion of patients achieving very good partial response (VGPR) or CR was not reached. The trial efficacy analysis used hierarchical sequence; thus, all secondary endpoints were considered exploratory. Secondary endpoint of median PFS was not estimable, but 18-month PFS was 85% for zanubrutinib (Brukinsa) and 84% for ibrutinib. Median OS was not estimable at the time of analysis, but 18-month OS was 97% for zanubrutinib (Brukinsa) and 93% for ibrutinib.
- C. Zanubrutinib (Brukinsa) had lower rates of atrial fibrillation (2% vs 15%), hypertension (11% vs 16%), minor bleeding (48.5% vs 59.2%), major hemorrhage (5.9% vs 9.2%), and diarrhea (20.8% vs 31.6%) compared to ibrutinib, respectively. The rate of neutropenia was 29.7% and 13.3% for zanubrutinib (Brukinsa) and ibrutinib, respectively.
- D. NCCN guidelines recommend the following preferred therapies for the treatment of primary, and previously treated, WM: bendamustine/rituximab, bortezomib/dexamethasone/rituximab, ibrutinib ± rituximab (category 1), rituximab/cyclophosphamide/dexamethasone, and zanubrutinib (Brukinsa) (category 1).

II. CLL/SLL:

- A. Efficacy and safety of zanubrutinib (Brukinsa) in treatment naïve CLL/SLL without a del17p mutation is established based on one Phase 3, open-label, randomized, active-controlled (cohort 1) trial (SEQUOIA). Enrolled patients (N=590) had untreated CLL/SLL, were ≥65 years of age or ≥18 years of age with comorbidities and were considered unsuitable for fludarabine-cyclophosphamide-rituximab treatment (defined as 65 years or older, a Cumulative Illness Rating Scale [CIRS] score of more than 6, creatinine clearance less than 70 mL/min, or history of severe or frequent infections). Patients in cohort 1 were without del17p mutation and were randomized 1:1 to zanubrutinib (Brukinsa) 160mg BID or bendamustine and rituximab (BR). Patients in cohort 2 (single-arm, open label portion of trial) had del17p mutation and underwent treatment with zanubrutinib (Brukinsa) by itself. As of December 2022, results are available for a median follow-up of 26.2 months. Median PFS and OS were not reached in any treatment group. Estimated PFS at 24 months was statistically superior for zanubrutinib (Brukinsa) as compared to BR (85.5% vs 69.5%)

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$p < 0.001$. In cohort 1, the difference in PFS between the treatment groups was not significant among patients with mutated IGHV, small subgroup of patients with SLL, and those with pathogenic TP53 mutation. Estimated OS at 24 months did not reach statistical significance between groups, (94.3% vs 94.6%) $p = 0.87$. The estimated PFS at 24 months for cohort 2 was 88.9%. Efficacy in patients with del17p mutation (cohort 2) remain undefined as results are considered observational due to lack of comparator arm. Grade 3 serious adverse events occurred more frequently in patients treated with BR than those treated with zanubrutinib (Brukinsa) (31% vs 20%). Incidence of Grade 3 neutropenia was higher with BR than zanubrutinib (Brukinsa) (22% vs 5%). Grade 1-2 bleeding and cardiac adverse events occurred more frequently with zanubrutinib (Brukinsa) than with BR (41% vs 9%) and (10% vs 6%), respectively. Several patients who reported major bleeding adverse events were treated with anticoagulants which may confound this safety data. Rates of cardiac arrhythmias with zanubrutinib (Brukinsa) in this study were consistent with those observed in other large, randomized studies of second-generation BTK inhibitors, including zanubrutinib (Brukinsa) and acalabrutinib (Calquence), in B-cell malignancies.

- B. Zanubrutinib (Brukinsa) was studied in one phase 1/2 open-label, dose expansion, single-arm trial of B-cell malignancies (BGB-3111-AU-003) in 101 patients with treatment relapsed/refractory CLL or SLL; one phase 2, open-label, single-arm trial (BGB-3111-205) in 91 Chinese patients with relapsed/refractory CLL or SLL; and one phase 3, randomized, open-label, head-to-head study against ibrutinib (ALPINE). The ALPINE study included 652 adult patients with relapsed/refractory CLL or SLL who have tried ≥ 1 prior systemic therapy consisting of ≥ 2 cycles of treatment. The median age was 67 years (range, 35 to 90), 73% had unmutated immunoglobulin heavy-chain variable region (IGHV) status, and 23% had a chromosome 17p deletion, TP53 mutation, or both. The median number of previous lines of therapy was 1 (range, 1 to 12). The percentage of patients with an overall response (ORR), as assessed by the independent review committee were higher in the zanubrutinib (Brukinsa) group than in the ibrutinib group (86.2% vs 75.7%). At 24 months, the percentage of patients with progression-free survival, as assessed by the investigators, was 78.4% (95% CI, 73.3 to 82.7) in the zanubrutinib (Brukinsa) group and 65.9% (95% CI, 60.1 to 71.1) in the ibrutinib group. Median progression-free survival was not reached in the zanubrutinib (Brukinsa) group and was 34.2 months (95% CI, 33.3 to not estimable) in the ibrutinib group. Results were consistent in the high-risk population of patients with 17p deletion, TP53 mutation, or both. The percentages of patients who were alive without disease progression at 24 months in the high-risk population were 72.6% (95% CI, 60.3 to 81.7) in the zanubrutinib (Brukinsa) group and 54.6 (95% CI, 40.7 to 66.4) in the ibrutinib group. As of the data-cutoff date in the final analysis, fewer deaths had been reported in the zanubrutinib (Brukinsa) group than in the ibrutinib group (48 and 60). Overall survival was not different in the two groups (hazard ratio for death 0.76; 95% CI, 0.51 to 1.11); longer follow-up is warranted to determine any differences between the treatments with respect to overall survival. The median overall survival had not been reached in either treatment group. Safety profile was comparable between the two treatment arms except, zanubrutinib (Brukinsa) had a higher incidence of Grade ≥ 3 adverse events compared to ibrutinib: neutropenia (16% vs 13.9%) and hypertension (14.8% vs 11.1%). There was a lower incidence of Grade ≥ 3 atrial fibrillation/flutter (1.9% vs 3.7%), serious events leading

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to treatment discontinuation (15.4% vs 22.2%) and events leading to death (10.2% vs 11.1%) in zanubrutinib (Brukinsa) vs ibrutinib treatment groups.

III. **Relapsed/refractory Follicular Lymphoma (FL)**

- A. Follicular lymphoma (FL) is the second most common non-Hodgkin lymphoma (NHL). It is a slow-growing B-cell lymphoproliferative disorder, with survival calculated in years rather than months. Prognosis is variable with some patients having waxing and waning disease that can last five or more years without therapy in a watch phase. Others with more disseminated disease and/or rapid tumor growth, require treatment before massive nodal and organ enlargement leads to pain, lymphatic obstruction or organ dysfunction.
- B. Long term survival can vary, but the five-year survival rate is about 90%, with 76-83% still living 10 years after diagnosis. Those that require a first line intervention have a high likelihood of a complete response; however, therapy is not curative and most patients will ultimately develop progressive disease. Patients relapsing over 24 months after initial chemotherapy, or over 12 months after single-agent rituximab, will have a clinically indolent course requiring intermittent treatment over decades and survival rates that mirror the general population. Modern therapy results in serial complete or partial remissions with treatment focusing on the alleviation of symptoms, reversal of cytopenias, and improvement of quality of life. Allogeneic hematopoietic cell transplantation (HCT) should be considered for all patients with relapsed FL; however, while curative of FL, this poses risks in itself such as graft versus host disease (GVHD) and survival rates are similar to patients who respond well to first line therapy. With each relapse, a histology should be rechecked as progression to a more aggressive lymphoma, such as diffuse large B cell lymphoma (DLBCL), requires a different treatment paradigm.
- C. Initial therapy for high tumor burden includes chemotherapy regimens such as CHOP or R-CHOP [cyclophosphamide, doxorubicin, vincristine, prednisone +/- obinutuzumab or rituximab], lenalidomide (Revlimid) plus rituximab, or bendamustine plus obinutuzumab or rituximab. Second-line therapy includes the same as first line recommendations, unless there is past bendamustine use, where that arm should not be retried. Additionally, second line treatment options include obinutuzumab monotherapy and lenalidomide (Revlimid) monotherapy or in combination with obinutuzumab. Patients may choose to stay on a long-term agent post first-line or second-line targeted therapy as well, which includes rituximab maintenance, obinutuzumab maintenance, or tazemetostat, or they may cease therapy to watch phase. Patients' refractory to two or more systemic therapies that have included an anti-CD20 monoclonal antibody (i.e., rituximab) and an alkylating agent (i.e., bendamustine, cyclophosphamide, chlorambucil), have the option of third line therapy. Third line includes bispecific antibody therapy, chimeric antigen receptor (CAR) T-cell therapy, tazemetostat, or zanubrutinib (Brukinsa) plus obinutuzumab. Most patients with more aggressive FL that experience serial relapses will be treated with many available agents at some point during their disease course covering multiple mechanisms of action. While relapsed FL is typically sensitive to additional therapy, the depth and duration of remission generally becomes shorter with each subsequent therapy.
- D. The efficacy of zanubrutinib (Brukinsa) plus obinutuzumab (Gazyva) for relapsed/refractory FL is from the Phase II trial, ROSEWOOD, an open-label, randomized, international study. Beginning in 2017, a total of 217 adult patients with a diagnosis of FL with failures of two or

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more systemic therapies for FL, including an anti-CD20 antibody and an alkylator-based combination therapy, with disease progression after completion of the most recent therapy or were refractory to therapy enrolled. Patients were randomized 2:1 for zanubrutinib (Brukinsa) 160mg twice daily plus intravenous (IV) obinutuzumab (Gazyva) [ZO, n=145] or monotherapy IV obinutuzumab (Gazyva) [O, n=72]. The primary endpoint read at the specified data cutoff timeline of 3 years and 11 months was overall response rate (ORR) done by PET-CT assessment. Secondary endpoints were tracked up to seven years and included duration of response (DOR), progression free survival (PFS), overall survival (OS), and time to next treatment (TTNT).

- E. At the primary analysis readout, ORR was significantly higher with ZO versus O, 69% to 46% with a risk difference of 23% (95% CI: 9,37; $p=0.001$). The ORR in the ZO arm was driven by both complete response and partial response with 39% and 30% respectively, while the ORR in the O arm was driven by partial response at 26% versus complete response at 19%. Secondary endpoints of DOR, TTNT, OS have not been fully realized due to sustained response with the ZO arm. For example, median TTNT in the ZO arm was not estimated as not all patients had required a next therapy, first reported TTNT was at 33.4 months versus the median TTNT in the O arm was 12.2 (8.5 to 17.3) months. Similarly, OS was also not estimable for the ZO arm as all patients were living versus some OS data in the O arm at 29.3 months and greater. Progression free survival also was not estimable in the combination arm of ZO reported as 28.0 months (16.1 to NE) with monotherapy O being 10.4months (6.5 to 13.8); HR of 0.50 (0.33 to 0.75) $p<0.001$.
- F. While ORR and PFS are surrogate endpoints in oncology, the use of TTNT lifts the confidence in this data. Follicular lymphoma (FL) is a non-curable disease with survival measured in years; the intent of treatment is to keep patients in remission and prevent disease progression. The combination therapy of ZO was able to achieve a higher ORR driven by the number of patients with complete response to therapy versus monotherapy O; as well as prolong the timeline for the TTNT by 21 months on average. Moreover, the data from PFS and OS was also in favor of the combination arm.

Investigational or Not Medically Necessary Uses

- I. The following indications do not have sufficient evidence to support the use of zanubrutinib (Brukinsa) at this time:
 - A. Previously untreated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma in patients with a del17p mutation
 - 1. The safety and efficacy in patients with del17p mutation was studied in cohort 2 (Group C) of the SEQUOIA trial. Estimated PFS at 24 months was 88.9% (95% CI: 81.3-93.6). Estimated OS at 24 months was 93.6% (95% CI: 87.1-96.9). Due to the open label, single-arm trial design with respect to the cohort 2 population, safety and efficacy remains observational and is undetermined at this time.
 - B. Diffuse Large B-cell Lymphoma (DLBCL)
 - C. Hairy Cell Leukemia (HCL)
 - D. Graft-versus Host Disease (GvHD)
 - E. Marginal Zone Lymphoma (MZL)

1. For the treatment of MZL, zanubrutinib (Brukinsa) is FDA-approved under the accelerated approval pathway based on ORR and DOR. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. Finalized data have not been published on these trials at this time.
2. Zanubrutinib (Brukinsa) was studied in one Phase 1/2 open-label, dose expansion, single-arm trial of B-cell malignancies including 20 previously treated MZL patients (BGB-3111-AU-003) and one Phase 2, open-label, multicenter, single-arm trial of 68 previously treated patients with MZL who had received at least 1 prior anti-CD20-based regimen (MAGNOLIA). MAGNOLIA study included patients with a median age of 70 years (range: 37 to 85), 38% had extranodal MZL, 38% nodal, 18% splenic and 6% had unknown subtype. The median number of prior systemic therapies was 2 (range: 1 to 6), with 88% of patients having prior rituximab-based chemotherapy, 32% had refractory disease at study entry. ORR was reached in 45 (68.2%) patients while DOR was not reached at the time of data analysis. Twelve-month DOR, PFS, and OS was as 93.0%, 82.5%, and 95.3%, respectively.
3. The most common adverse events were similar to adverse events seen in clinical trials studying other cancer types and included diarrhea, contusion, constipation, pyrexia, and upper respiratory tract infections. Serious adverse events occurred in 38.2% of patients and included COVID-19 pneumonia, pyrexia, and fall. Four patients discontinued treatment due to adverse events and 29.4% of patients had dose interruption due to adverse events.
4. Treatment of MZL with zanubrutinib (Brukinsa) remains experimental and investigational. The quality of evidence is considered low due to observational nature of clinical trials (single-arm, open-label study designs) with unknown clinical impact on the overall survival rate, health-related quality of life, or symptom improvement in treated patients. Confirmatory trials are needed to definitively establish benefit and value of this agent in MZL.
5. NCCN guidelines recommend anti-CD20 based regimens as preferred therapies in second-line and subsequent setting as well as CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) ibrutinib, lenalidomide + rituximab, and zanubrutinib with a Category 2A recommendation. Other recommend regimens additionally umbralisib and PI3K inhibitors in patients relapsed/refractory after 2 prior therapies.

F. Indolent Non-Hodgkin Lymphoma (iNHL)

G. MCL monotherapy

1. For the treatment of MCL, zanubrutinib (Brukinsa) was FDA-approved under the accelerated approval pathway based on overall response rate (ORR). Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials; however, finalized data has not been published on these trials at this time.
2. Zanubrutinib (Brukinsa) was studied in one open-label, single-arm, Phase 2 trial (BGB-3111-206), and one Phase 1/2 safety and pharmacokinetic trial (BGB-3111-AU-003) in 118 patients with MCL who had progressed on prior systemic therapy.

The primary efficacy outcome was ORR which was 84% in both trials. Secondary efficacy outcomes were complete response (CR), partial response (PR), and duration of response (DOR). The percentage of patients with a CR was 59% and 22% for the Phase 2 trial and Phase 1/2 trial, respectively. The percentage of patients with a PR was 24% and 62% for the Phase 2 trial and Phase 1/2 trial, respectively. Median DOR in months was 19.5 and 18.5 for the Phase 2 trial and Phase 1/2 trial, respectively. Progression-free survival was evaluated in the Phase 2 trial and found 74.6% of patients at 12 months were progression-free.

3. Treatment of MCL with zanubrutinib (Brukinsa) remains experimental and investigational. The quality of evidence is considered low due to observational nature of clinical trial (single-arm, open-label study design) with unknown clinical impact on the overall survival rate, health-related quality of life, or symptom improvement in treated patients. Confirmatory trials are needed to definitively establish benefit and value of this agent in MCL.

- H. MCL first-line therapy
- I. MCL combination therapy
- J. Richter's Transformation

** The Moda Split Fill program is a physician-centric, patient engagement program intended to provide enhanced patient and physician support while accomplishing the goals of minimizing waste and avoiding incremental healthcare costs due to medication intolerance and unexpected change or termination of therapy regimen. Under the Split Fill program, the identified medications are programmed for fills of up to a 14 or 15-day supply for the duration of the first three months (86 or 90 days) of therapy. This program affords additional interactions with a specialty pharmacist, allowing more frequent assessments of side effects and barriers to adherence. Each fill is administered at half of the member cost-share, thereby reducing the economic burden if they must discontinue therapy mid-month.*

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Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
lenalidomide (Revlimid®); pomalidomide (Pomalyst®); thalidomide (Thalomid®)	Follicular Lymphoma
tazemetostat (Tazverik™)	
ibrutinib (IMBRUVICA®)	Waldenström Macroglobulinemia
ibrutinib (IMBRUVICA®)	
idelalisib (Zydelig®)	Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)
pirtobrutinib (Jaypirca™)	
venetoclax (Venclexta®)	
duvelisib (Copiktra®)	
acalabrutinib (Calquence®)	

Policy Implementation/Update:

Action and Summary of Changes	Date
Added Brukinsa tablets to QL table	08/2025
Revised renewal criteria for clarity	02/2025
Addition of related policies table. Addition of coverage for follicular lymphoma.	12/2024
Removed criterion requiring use of other BTKi before Brukinsa in relapsed/refractory CLL/SLL. Added previously untreated CLL/SLL indication and associated criteria. Added previously untreated CLL/SLL with del17p mutation as E/I. Changed the length of initial approval from three to six months. Updated supporting evidence section.	12/2022
Removed initial criteria and moved MCL indication to experimental or not medically necessary uses section.	01/2022
Added initial criteria for non-FDA approved indication of CLL/SLL and updated supporting evidence. Added Richter's Transformation in the E/I section.	12/2021
Added expanded indication of Waldenström's macroglobulinemia (WM) in the initial evaluation criteria. Updated supporting evidence section to include clinical trial information for WM. Added supporting evidence for the expanded indication of marginal zone lymphoma (MZL) in investigational uses section.	11/2021
Policy created	02/2020

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP293

Description

Zilucoplan (Zilbrysq) a targeted C5 complement inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
zilucoplan (Zilbrysq)	Myasthenia Gravis	16.6 mg/0.416 mL	11.648 mL/28 days
		23 mg/ 0.574 mL	16.072 mL/28 days
		32.4 mg/ 0.81 mL	22.68 mL/28 days

Initial Evaluation

- I. **Zilucoplan (Zilbrysq)** may be considered medically necessary when the following criteria are met:
 - A. Member is 18 years of age or older; **AND**
 - B. Medication is prescribed by, or in consultation with, a specialist (e.g., neurologist or rheumatologist); **AND**
 - C. Medication will not be used in combination with maintenance immunoglobulin therapy (IVIG), rituximab, or another biologic for gMG [i.e., eculizumab (Soliris), ravulizumab (Ultomiris), efgartigimod alfa (Vyvgart), rozanolixizumab (Rystiggo)]
 - D. A diagnosis of **generalized myasthenia gravis (gMG)** when the following are met:
 1. Provider attestation that the member is acetylcholine receptor antibody positive (AChR-AB+); **AND**
 2. Provider attestation that the member has Myasthenia Gravis Foundation of America (MGFA) Clinical Classification class II to IV disease (i.e., not defined as ocular myasthenia gravis and not intubated); **AND**
 3. Member has a baseline MG-activities of daily living (MG-ADL) score ≥ 6 ; **AND**
 - E. Member has had an inadequate response (e.g., unable to maintain baseline MG-ADL score) after a minimum of one-year trial of each of the following therapies, unless both were not tolerated or contraindicated:
 1. Acetylcholinesterase inhibitor (e.g., pyridostigmine); **AND**
 2. An oral immunosuppressant (e.g., azathioprine, cyclosporine, mycophenolate, low dose daily glucocorticoids); **OR**
 - F. Member required chronic treatment with plasmapheresis or plasma exchange or intravenous immunoglobulin (IVIG) in addition to immunosuppressant therapy; **AND**
 - G. Member will be continuing on standard of care therapies (e.g., pyridostigmine, azathioprine, low dose daily glucocorticoids) unless all are contraindicated or not tolerated

- II. Zilucoplan (Zilbrysq) is considered investigational when used for all other conditions, including but not limited to:
- A. Ocular Myasthenia Gravis
 - B. Myasthenia Gravis MUSK antibody positive or other antibodies that are not AChR
 - C. Pediatric Myasthenia Gravis
 - D. Postural Orthostatic Tachycardia Syndrome
 - E. Primary Immune Thrombocytopenia
 - F. Paroxysmal Nocturnal Hemoglobinuria

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
- II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. Provider attests that the member continues to have a clinical response to zilucoplan (Zilbrysq) (i.e., an improvement in the MG-ADL score, a reduction/elimination of oral steroids/immunosuppressants required, etc.); **AND**
- IV. Medication will not be used in combination with maintenance immunoglobulin therapy (IVIG), rixtuximab, or another biologic for gMG [i.e., eculizumab (Soliris), ravulizumab (Ultomiris), efgartigimod alfa (Vyvgart), rozanolixizumab (Rystiggo)]

Supporting Evidence

- I. Zilucoplan (Zilbrysq) is FDA approved to treat adult patients with generalized myasthenia gravis (gMG) that are anti-acetylcholine receptor antibody positive (AChR-AB+). Use in individuals under the age of 18 years as well as use in other antibody positive patients has not been determined to be safe and effective at this time.
- II. Due to the complexity of diagnosing and treating gMG, zilucoplan (Zilbrysq) must be prescribed by, or consultation with, a specialist in neurology or rheumatology.
- III. Myasthenia gravis is a chronic, autoimmune, neuromuscular disease characterized by fluctuating motor weakness involving the ocular, spinal column, limb and/or respiratory muscles. The weakness is due to an antibody-mediated, immunologic attack directed at the postsynaptic membrane of the neuromuscular junction (acetylcholine receptors [AChR] or receptor associated proteins, such as MUSK) led by an IgG immune response. This causes common symptoms such as drooping eyelids (ptosis) and double vision (diplopia), muscle weakness and fatigue, trouble swallowing or pronouncing words, and facial muscle involvement causing a mask-like appearance or sneer.
- IV. AChR are the most common receptor affected; about 85% of patients will test positive for AChR antibodies, which is considered a positive indicator of a MG diagnosis. Those who do not test positive for AChR, may then test positive for a different receptor protein, such as muscle-specific tyrosine kinase (MuSK) or LR4 antibody. AChR antibody (AChR-AB) negative patients do not tend to respond as well to regular standards of care as the AB positive patients do and tend to respond better to rituximab (Inflectra) instead.

- V. Additionally, there are two clinical forms of MG: ocular and generalized. Although the majority of patients present with a vision symptom as the first indicator of MG, roughly 15% of patients remain as ocular MG, while the rest become generalized MG. Those with ocular MG are less likely to be AchR-AB positive and have mixed response to traditional therapies usually favoring eye patches or eye “crutches” to assist with drooping eyelids, and in severe cases, surgery.
- VI. Clinical presentation of MG is staged by ocular versus generalized and the severity of their symptoms. Stage I is ocular only and Stage V is those patients who require intubation; Stages II-IV encompass those patients in between as mild to moderate and the systems involved. MG are further assessed by two common scoring systems: the Quantitative Myasthenia Gravis (QMG) and the MG activity of daily living (MG-ADL). Both are quality of life scales assessing muscle strength and weakness, higher scores on each scale indicate more severe disease. QMG is a 13-item scale with a possible worst score of 39 and MG-ADL is an 8-item scale with a possible worst score of 24. Based on clinical data and physician input, a three-point change is clinically meaningful in QMG for moderate-severe presentation and a two-point change for milder presentation; a two-point change is clinically meaningful in MG-ADL for mild-moderate, there is not an agreement on severe patients in the MG-ADL scale.
- VII. Currently there is no cure for MG, patients tend to reach their peak in symptoms and severity within the first three years of diagnosis and then stabilize or move into remission. Available treatments control symptoms and prevent relapses allowing patients to live a relatively high quality of life with a normal life expectancy. Treatment options include symptomatic treatment (e.g., acetylcholinesterase inhibitors [e.g., pyridostigmine]), corticosteroids, long-term immunosuppressive therapy (e.g., azathioprine, cyclosporine, methotrexate), plasma exchange, and rapid immunomodulating treatments (e.g., immune globulin IV). Thymectomy is also an option and according to the Internal Consensus Guidelines on MG 2020, thymectomy should be considered early in the disease for those under 50 years of age with generalized MG or those who fail to respond to an adequate trial of immunotherapy and have stable MG amenable to surgery (i.e., no current flares, on stable dose of medications without changes being made). The only biologic treatment currently included in these same guidelines is eculizumab (Soliris), also a C5 inhibitor, which is recommended in the treatment of severe, refractory, AchR-AB+ gMG. Internal Consensus Guidelines define refractory disease as an unchanged or worse MG-ADL/QMG after corticosteroids and at least two other immunosuppressant agents. The presence of persistent symptoms or side effects that limit functioning after treatment used at the maximum dose the patient is able to tolerate for an adequate duration (typically 12 weeks).
- VIII. Pyridostigmine is recommended as initial therapy and unless not tolerated. Patients should remain on this therapy lifelong as a standard of care. The ability to discontinue pyridostigmine can be indicative of meeting therapy goals and may guide tapering of other drugs. For patients that continue to experience bothersome symptoms, next line agents include nonsteroidal immunosuppressants (NISTs) such as azathioprine, cyclosporine, mycophenolate mofetil, methotrexate, and tacrolimus. NIST can be used in combination with a corticosteroid (prednisone) for flares or more rapid deceleration of exacerbation/crisis. Myasthenia crisis can occur from concurrent infection, surgery, pregnancy, and certain medication classes. Mild flares may simply respond to changes in standard of care doses or frequency, such as increasing pyridostigmine, or beginning a course of prednisone. More severe cases where patients are experiencing increased dysphagia or dyspnea, initiation of intravenous immune globulin (IVIG) or plasmapheresis, are used to return to clinical baseline.

- IX. The safety and efficacy of zilucoplan (Zilbrysq) was evaluated in RAISE, a Phase 3 multicenter, randomized, double-blind, placebo-controlled study. The trial evaluated 174 AChR-Ab+ adult patients with gMG between Stage II-IV. All patients had a MG-ADL score ≥ 6 and were randomized 1:1 to receive either placebo (n=88) or 0.3mg/kg zilucoplan (Zilbrysq, n=86) SC daily over 12 weeks. Patients were required to remain on standard-of-care therapies during the study that they were on preceding the trial start (i.e., pyridostigmine, NISTs) so long as there was not a change in dose or frequency or an anticipated need to change during the 12-week study. Approximately 85% of patients were on pyridostigmine, 63% steroids, and 51% NISTs. Data was considered missing if rescue therapy for a crisis or relapse was required. MG-ADL response was the primary endpoint at the end of week 12.
- X. A statistically significant difference favoring zilucoplan (Zilbrysq) over placebo was seen at the end of the 12-week trial. Patients taking zilucoplan (Zilbrysq) had a change of 4.39 points versus 2.30 in placebo of the MG-ADL score [-2.09 (-3.24, -0.95); $p < 0.001$]. Secondary endpoints looked at additional standard improvement/severity scales such as response in QMG, MGC, and MG-QoL 15r scores. These also met a statistically different response in zilucoplan (Zilbrysq) versus placebo. A total of 200 patients enrolled into the ongoing extension trial (RAISE-XT). RAISE-XT was primarily a safety extension trial, but secondary endpoints continued to monitor the endpoints of RAISE. These endpoints were maintained or improved at the interim data analysis at week 90. There were no new safety signals at week 90.
- XI. There are currently four other biologics approved in the treatment of MG; two complement factors: eculizumab (Soliris) and racuzumab (Ultomiris) and two neonatal Fc receptor (FcRn) inhibitors: efgartigimod (Vyvgart) and rozanolixizumab (Rystiggo). The Internal Consensus Guidelines on Myasthenia Gravis 2020 recommend eculizumab (Soliris) in refractory MG after failure of IVIG, plasmapheresis, and immunosuppressive agents. The exclusion criteria of all four of these trials did not allow concurrent use of each other or IVIG, plasmapheresis, or rituximab within at least four weeks of the trial onset. The combination use of any of these therapies would be considered experimental.

Investigational or Not Medically Necessary Uses

- I. Zilucoplan (Zilbrysq) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Ocular Myasthenia Gravis
 - B. Myasthenia Gravis MUSK antibody positive or other antibodies that are not AChR
 - C. Pediatric Myasthenia Gravis
 - D. Postural Orthostatic Tachycardia Syndrome
 - E. Primary Immune Thrombocytopenia
 - F. Paroxysmal Nocturnal Hemoglobinuria

Appendix

I. MGFA Clinical Classification:

Class	Distribution and Severity	
1	Any ocular muscle weakness, all other muscle strength is normal	
2	Mild, generalized	• 2a: Mainly limb, axial muscles

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		• 2b: mainly oropharyngeal/respiratory muscles
3	Moderate, generalized	• 3a: Mainly limp, axial muscles • 3B: Mainly oropharyngeal/respiratory muscles
4	Severe, generalized	• 4a: Mainly limp, axial muscles • 4B: Mainly oropharyngeal/respiratory muscles
5	Intubation	

II. MG-ADL Score:

	Score=0	Score=1	Score=2	Score=3	Your Score
Talking	Normal	Intermittent slurring or nasal speech	Constant slurring or nasal speech, but can be understood	Difficult to understand speech	
Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube	
Swallowing	Normal	Rare episode of choking	Frequent choking necessitating changes in diet	Gastric tube	
Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilatory dependence	
Brushing teeth or hair	Normal	Extra effort, but no rest periods needed	Rest periods needed	Cannot do one of these functions	
Arising from chair	Normal	Mild, sometimes uses arms	Moderate, always uses arms,	Severe, requires assistance	
Double vision	Normal	Occurs, but not daily	Daily, but not constant	Constant	
Eyelid droop	Normal	Occurs, but not daily	Daily, but not constant	Constant	
Total Score=					

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Related Policies

Currently there are no related pharmacy policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	02/2024

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP285

Description

Zuranolone (Zurzuvae) is an orally administered neuroactive steroid GABA_A receptor positive allosteric modulator.

Length of Authorization

- Initial: One time fill
- Renewal: No renewal

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
zuranolone (Zurzuvae)	Postpartum depression	20mg capsule	28 capsules/14 days
		25mg capsule	
		30mg capsule	14 capsules/14 days

Initial Evaluation

- I. **Zuranolone (Zurzuvae)** may be considered medically necessary when the following criteria are met:
 - A. Member is 18 years of age or older; **AND**
 - B. A diagnosis of **Postpartum Depression** when the following are met:
 1. Member has moderate to severe depressive symptoms as demonstrated by an objective measurement scale score consistent with severe designation (e.g., HAMD-17, MADRS, PHQ-9, etc.); **AND**
 2. Member experienced onset of depressive symptoms during the third trimester of pregnancy OR within the first four weeks after delivery; **AND**
 3. Request is within 12 months of delivery; **AND**
 4. Member has discontinued breastfeeding; **OR**
 - i. Member has agreed to temporarily hold breastfeeding for course of therapy and one week following; **AND**
 5. Treatment with at least one SSRI (e.g., citalopram [Celexa], escitalopram [Lexapro], fluoxetine [Prozac], sertraline [Zoloft], etc.) OR SNRI (e.g., duloxetine [Cymbalta], desvenlafaxine succinate [Pristiq], venlafaxine [Effexor], etc.) has been ineffective, contraindicated, or not tolerated.
- II. Zuranolone (Zurzuvae) is considered not medically necessary when criteria above are not met and/or when used for:
 - A. Major Depressive Disorder (MDD)
- III. Zuranolone (Zurzuvae) is considered investigational when used for all other conditions, including but not limited to:
 - A. Use in the pediatric population
 - B. Depressive episodes in bipolar II disorder

- C. Episodic treatment of MDD and/or PPD
- D. Treatment resistant depression
- E. Other psychiatric disorders

Renewal Evaluation

- I. Zuranolone (Zurzuvae) is not eligible for renewal.

Supporting Evidence

- I. The safety and efficacy of zuranolone (Zurzuvae) was evaluated in a total of five phase 3 randomized, double-blind, placebo-controlled trials that made up two clinical programs. The LANDSCAPE clinical program (MOUNTAIN, WATERFALL, CORAL) focused on major depressive disorder (MDD), while the NEST clinical program (ROBIN, SKYLARK) focused on postpartum depression (PPD). As of February 2025, the FDA has only approved zuranolone (Zurzuvae) for treatment of PPD.
- II. Zuranolone (Zurzuvae) was studied in adult patients aged 18 and older and has not been evaluated for safety and/or efficacy in pediatric patients.
- III. **PPD**
 - The SKYLARK trial was a randomized, double-blind, placebo-controlled trial that evaluated the safety and efficacy of a single 14-day course of zuranolone 50mg compared to placebo in adult women with severe postpartum depression, as evidenced by a baseline HAM-D-17 score of at least 26, who had onset of depressive symptoms during the third trimester or first four weeks after delivery. All patients were required to be within 12 months postpartum. The primary efficacy endpoint was change from baseline in HAM-D-17 score at day 15, which was met (LS means, -15.6 (0.80) vs. -11.6 (0.89), p=0.007).
 - Patients who were actively breastfeeding were excluded from participation in the clinical trials. To be included, patients were required to have either completely ceased breastfeeding or agreed not to provide breastmilk to their infant(s) from just prior to receiving the study drug on day one of the trial period until seven days after the last dose of the study drug. Data from a Phase 1, single-center, open-label study conducted in healthy, lactating adult females that was designed to evaluate the pharmacokinetics and safety of zuranolone (Zurzuvae) demonstrated that the estimated relative infant dose (RID), calculated as the infant dose divided by the maternal dose, was 0.357% on day 5 and the estimated daily infant dose was 0.00124 mg/kg/day. The estimated mean RID was consistent with a low fraction of unbound zuranolone (Zurzuvae) in plasma ($\leq 0.52\%$). Maternal milk production decreased by 8.3% (41.2 [140.11] mL) in volume collected at day five compared to baseline. Investigators noted that the interpretation of the effect of zuranolone (Zurzuvae) on milk production is limited due to variability inter-patient milk production at baseline, lack of placebo control, and the small sample size (N=15).
- IV. The majority of TEAEs observed throughout the clinical program were considered mild or moderate in severity, with serious adverse events (SEAs) occurring in <2% of zuranolone (Zurzuvae) treated patients. Across the clinical program, there was no observed increase in

incidence of suicidal ideation. The most common TEAEs (>5%) include headache, somnolence, dizziness, nausea, sedation, fatigue, and diarrhea.

- V. For treatment of PPD, the American Academy of Family Physicians (AAFP) and National Institute for Health (NIH) recommend psychotherapy alone for mild-to-moderate PPD and pharmacologic treatment with select SSRIs and SNRIs for moderate-to-severe PPD. The antidepressants recommended for PPD include citalopram, escitalopram, fluoxetine, paroxetine, sertraline, desvenlafaxine, duloxetine, venlafaxine, and bupropion. While these antidepressants generally provide some symptom improvement within the first week of use, full therapeutic effects may not be realized until 4-6 weeks after initiation. Given that zuranolone (Zurzuva) demonstrated symptom improvement as early as 2-days after first dose and clinically meaningful improvement by day 15 in clinical trials, an exception may be considered in cases of severe PPD where faster onset of action is clinically warranted.
- Brexanolone (Zulresso) is an IV-administered neuroactive steroid GABAA receptor positive allosteric modulator that FDA-approved in the setting of PPD. This 60-hour continuous infusion is currently recommended by UpToDate for patients with severe PPD who prioritize fast onset of action and should be followed by a guideline-recommended SSRI or SNRI as maintenance therapy. As of July 2023, guidelines have not been updated to include brexanolone (Zulresso) or zuranolone (Zurzuva), so there is minimal insight as to the appropriate use of zuranolone (Zurzuva) following prior treatment with brexanolone (Zulresso) in the current or previous episode of PPD.

Investigational or Not Medically Necessary Uses

- I. Zuranolone (Zurzuva) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
- A. Major Depressive Disorder
- i. The safety and efficacy of zuranolone (Zurzuva) in the setting of adult patients with severe MDD was evaluated in the LANDSCAPE clinical program, which is made up of three clinical trials: the MOUNTAIN, WATERFALL, and CORAL clinical trials. The MOUNTAIN and WATERFALL clinical trials evaluated zuranolone (Zurzuva) as either monotherapy or adjunct to antidepressant therapy, as long as they were established on therapy on a stable antidepressant dose for at least 60 days prior to baseline. The CORAL clinical trial evaluated zuranolone (Zurzuva) when co-initiated with standard of care antidepressant therapy. The primary endpoint in all trials was the change from baseline (CFB) in the baseline Hamilton Depression Rating Scale (HAM-D-17) at day 15, with the exception of the CORAL trial which evaluated this endpoint at day 3. The primary endpoint was statistically significant in favor of zuranolone (Zurzuva) in the WATERFALL (least square mean [LSM] change, -14.1 [SE=0.5] vs. -12.3 [SE=0.5], p=0.01) and CORAL (LSM change, -8.9 vs. -7.0, p=0.004) clinical trials, but not the MOUNTAIN clinical trial.
 - ii. Although the results of the LANDSCAPE clinical program demonstrated statistically significant change from baseline in HAM-D-17 scores, this did not correlate to a clinically meaningful change compared to placebo, defined as a difference of 4 or more points on the HAM-D-17 scale. Due to a lack of clinically meaningful impact

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on depressive symptoms compared to placebo, the value of zuranolone (Zurzuvae) as compared to standard of care antidepressant therapy remains undefined at this time.

- iii. On August 4, 2023, the FDA released a complete response letter (CRL) for the new drug application (NDA) for zuranolone (Zurzuvae) for the MDD indication. The CRL stated that the application did not provide substantial evidence of effectiveness to support approval of zuranolone (Zurzuvae) for the treatment of MDD, and that an additional study or studies will be needed. Given variable primary endpoint results and lack of clinically meaningful impact on depressive symptoms compared to placebo throughout the clinical program, treatment of MDD with zuranolone (Zurzuvae) is not medically necessary.

B. Use in the pediatric population

C. Depressive episodes in bipolar II disorder

D. Episodic treatment of MDD and/or PPD

- i. As of August 2023, zuranolone (Zurzuvae) has only been approved as a single treatment course for treatment of PPD. Zuranolone (Zurzuvae) is also being evaluated in an ongoing, open-label, phase 3, observational trial evaluating the safety and tolerability of an initial course of zuranolone (Zurzuvae) 30mg or 50mg and the need for repeat courses in adults with MDD for up to 1 year. At the primary cutoff point in November 2021, zuranolone (Zurzuvae) appeared to generally well tolerated, with reported treatment emergent adverse events (TEAEs) consistent with existing clinical trial data. Most patients in the zuranolone (Zurzuvae) 50mg cohort received one or two total treatment courses during the study period, up to one year (79.5% [116/146]), with median time to first repeat treatment course of 249 days. There are no studies currently underway to evaluate episodic treatment in PPD.

E. Treatment resistant depression

F. Other psychiatric disorders

References

1. Hirst KP, Moutier CY. Postpartum Major Depression. Am Fam Physician. 2010;82(8):926-933.
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3. American Psychological Association. (2019). Clinical practice guideline for the treatment of depression across three age cohorts. Retrieved from <https://www.apa.org/depression-guideline>
4. Clayton AH, Lasser R, Nandy I, et al. Zuranolone in Major Depressive Disorder: Results from MOUNTAIN – A Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial. J Clin Psychiatry 2023;84(2):22m14445.
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7. Viguera A, et al. Severe postpartum unipolar major depression: Choosing treatment. UpToDate. Last updated March, 14, 2023. Accessed from: https://www.uptodate.com/contents/severe-postpartum-unipolar-major-depression-choosing-treatment?search=postpartum%20depression%20treatment&source=search_result&selectedTitle=2~145&usage_type=default&display_rank=2.

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8. Treatment and Management of Mental Health Conditions During Pregnancy and Postpartum: ACOG Clinical Practice Guideline No. 5. Obstet Gynecol. 2023;141(6):1262-1288. doi:10.1097/AOG.0000000000005202.
9. Screening and Diagnosis of Mental Health Conditions During Pregnancy and Postpartum: ACOG Clinical Practice Guideline No. 4. Obstet Gynecol. 2023;141(6):1232-1261. doi:10.1097/AOG.0000000000005200.

Related Policies

Policy Name	Disease state
esketamine (Spravato™) Policy	Treatment resistant depression (TRD) and Depressive symptoms in adults with major depressive disorder (MDD) with acute suicidal ideation or behavior

Policy Implementation/Update:

Action and Summary of Changes	Date
Annual Review; Added criterion to allow coverage in moderate to severe depression, use within 12 months postpartum, and renewal evaluation	02/2025
Policy created	08/2023

Please see the UMP Preferred Drug list for more details on prescription drugs that have step requirements:

PEBB	https://ump.regence.com/pebb/benefits/prescriptions
SEBB	https://ump.regence.com/sebb/benefits/prescriptions