

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: UMP036

Description

The listed treatments for Hepatitis C are for orally administered Direct-Acting Antiviral (DAA) therapies.

Length of Authorization

- Initial: 8-16 weeks based on liver status*
- Renewal: none

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit*
glecaprevir/pibrentasvir (Mavyret)	100 mg/40 mg tablet	HCV Genotype 1, 2, 3, 4, 5, 6 Treatment naïve or experienced	84 tablets/28 days
	50mg/20mg oral pellets		140 packets/28 days
sofosbuvir (Sovaldi)	200 mg oral tablet	HCV Genotype 2 or 3 Treatment naïve or experienced	28 tablets/28 days
	400 mg oral tablet	HCV Genotype 1, 2, 3, 4 Treatment naïve or experienced	
ledipasvir/sofosbuvir (Harvoni)	45 mg /200 mg tablet	HCV Genotype 1, 4, 5, 6 Treatment naïve or experienced	28 tablets/28 days
	90 mg /400 mg tablet	HCV Genotype 1, 2, 3, 4, 5, 6 Treatment naïve or experienced	
ledipasvir/sofosbuvir (authorized generic)	45 mg /200 mg tablet	HCV Genotype 1, 4, 5, 6 Treatment naïve or experienced	28 tablets/28 days
	90 mg /400 mg tablet	HCV Genotype 1, 2, 3, 4, 5, 6 Treatment naïve or experienced	
velpatasvir/sofosbuvir (Epclusa)	50 mg / 200 mg tablet	HCV Genotype 1, 2, 3, 4, 5, 6 Treatment naïve or experienced	56 tablets/28 days
	100 mg/ 400 mg tablet		28 tablets/28 days
	150mg/37.5mg oral pellets		28 packets/28 days
	200mg/50mg oral pellets		56 packets/28 days

velpatasvir/sofosbuvir (authorized generic)	100 mg/400 mg tablet	HCV Genotype 1, 2, 3, 4, 5, 6 Treatment naïve or experienced	28 tablets/28 days
daclatasvir (Daklinza)	30 mg, 60 mg, 90 mg tablet	HCV Genotype 1, 3	28 tablets/28 days
elbasvir/grazoprevir (Zepatier)	50 mg /100 mg tablet	HCV Genotype 4	28 tablets/28 days
velpatasvir/sofosbuvir/voxilaprevir (Vosevi)	100 mg/400 mg/100 mg tablet	HCV Genotype 1, 2, 3, 4, 5, 6 Treatment experienced	28 tablets/28 days
simeprevir (Olysio)	150 mg capsule	HCV Genotype 1 Treatment naïve or experienced	28 capsules/28 days
ombitasvir/paritaprevir/ritonavir/dasabuvir (Viekira Pak)	12.5/75/50 mg oral tablet and dasabuvir 250 mg tablet	HCV Genotype 1a, 1b Treatment naïve or experienced	1 box/ 28 days
ombitasvir/paritaprevir/ritonavir/dasabuvir (Viekira XR)	12.5/75/50 mg oral tablet and dasabuvir 250 mg tablet	HCV Genotype 1a, 1b Treatment naïve or experienced	1 box/28 days
ombitasvir/paritaprevir/ritonavir (Technivie)	12.5/75/50 mg tablet	HCV Genotype 4	1 box/28 days

*See appendix for specific treatment durations

Initial Evaluation

glecaprevir/pibrentasvir (Mavyret) is the preferred Direct-Acting Antiviral (DAA) therapy

- **Patients must have failed, have contraindication to, or intolerance of glecaprevir/pibrentasvir (Mavyret) prior to the consideration of any other Direct-Acting Antiviral (DAA) therapy.**
 - There is no prior authorization required for the preferred Direct-Acting Antiviral (DAA) therapy unless requesting above the quantity limit noted above.

- I. **Non preferred Hepatitis C treatments** may be considered medically necessary when the following criteria are met:
 - A. Patient has confirmed diagnosis of Hepatitis C and a quantifiable HCV RNA test >15 IU/mL within the last 12 months; **AND**
 - B. Required documentation for confirmation of treatment duration, as confirmed by a clinical pharmacist, include:
 1. HCV Genotype; **AND**
 2. Current HCV RNA viral load less than 12 months old; **AND**
 3. Fibrosis staging test (e.g FibroScan or FibroSure) to determine liver fibrosis results LESS than 2 years old required to ensure the appropriate treatment regimen is

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used (e.g. patients with cirrhosis and/or decompensation may require longer treatment and/or ribavirin); **AND**

4. If fibrosis level F4 (cirrhosis): Documentation decompensated or previous episodes of decompensated liver disease; **AND**
5. Documentation of treatment history including:
 - i. Prior treatment regimen; **AND**
 - ii. Duration of prior treatment; **AND**
 - iii. Response to treatment; **AND**
 - iv. Dates of prior treatment; **AND**
6. Documentation, if available, of the presence or absence of resistant mutations in treatment experienced patients; **AND**
7. Documented rationale why treatment with preferred product glecaprevir/pibrentasvir (Mavyret) is not appropriate; **AND**
8. If the request is for **Vosevi** the member meets one of the specific settings below:
 - i. Member has previously failed treatment with elbasvir-grazoprevir (Zepatier) or glecaprevir/pibrentasvir (Mavyret); **OR**
 - ii. Member has HCV genotype 3 and was previously treated with sofosbuvir

II. Treatment for Hepatitis C is considered not medically necessary when criteria above are not met and/or in members who:

- A. Are taking medications that are contraindicated with, or that have a severe drug interaction with, the prescribed HCV treatment.
- B. Are pregnant or planning on becoming pregnant
- C. Have severe end organ disease and are not eligible for transplantation (e.g. heart, lung, kidney)
- D. Have a clinically-significant illness or any other major medical disorder that may interfere with patients' ability to complete a course of treatment.
- E. In the professional judgment of the primary treating clinician, those who would not achieve a long-term clinical benefit from HCV treatment (e.g. patients with multisystem organ failure, receiving palliative care, with significant pulmonary or cardiac disease, or with malignancy outside of the liver not meeting oncologic criteria for cure).
- F. Have a MELD score <20 and one of the following:
 1. Cardiopulmonary disease that cannot be corrected and is a prohibitive risk for surgery
 2. Malignancy outside the liver not meeting oncologic criteria for cure
 3. Hepatocellular carcinoma with metastatic spread
 4. Intrahepatic cholangiocarcinoma
 5. Hemangiosarcoma
 6. Uncontrolled sepsis

Supporting Evidence

Chronic Hepatitis C Infection

- I. Elbasvir/grazoprevir (Zepatier) and glecaprevir/pibrentasvir (Mavyret) are the only agents that have been studied in severe renal impairment (CrCl < 30 mL/min) and ESRD.

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- II. In August 2019, the FDA released a statement around the use of Mavyret, Zepatier, or Vosevi to treat chronic hepatitis C in patients with moderate to severe liver impairment (Child-Pugh B or C) which resulted in rare cases of worsening liver function or liver failure. In the warning, the FDA adds that health care professionals should continue to prescribe Mavyret, Zepatier, or Vosevi as indicated in the prescribing information for patients without liver impairment or with mild liver impairment (Child-Pugh A).
- III. Patients with HCV infection who have decompensated cirrhosis—moderate or severe hepatic impairment (Child-Pugh B or C) — should be referred to a medical practitioner with expertise in that condition, ideally in a liver transplant center. AASLD guidelines recommend ledipasvir/sofosbuvir (Harvoni), velpatasvir/sofosbuvir (Epclusa), or daclatasvir (Daklinza) plus sofosbuvir (Sovaldi) in this setting.

Acute Hepatitis C Infection

- I. Acute HCV is defined by active infection for no more than six months since the first encounter. Acute HCV is often asymptomatic or shows nonspecific symptoms (e.g., fatigue, anorexia, mild or moderate abdominal pain, low-grade fever, nausea, and/or vomiting) that frequently are not recognized as being associated with acute HCV infection. Less than 25% of patients with acute HCV will have jaundice. Acute HCV infections may spontaneously clear in 20% to 50% of patients. Early intervention in patients with HCV infection prevents progression to chronic disease and eventually cirrhosis or liver cancer. The 2023 American Association for the Study of Liver Diseases (AASLD)— Infectious Diseases Society of America (IDSA) guidelines for HCV recommends that patients with acute HCV infection should be treated upon initial diagnosis without awaiting spontaneous resolution. Despite lack of FDA approval, the guidelines recommend treatment of acute HCV with therapies FDA approved for chronic HCV (e.g. glecaprevir/pibrentasvir (Mavyret), velpatasvir/sofosbuvir (Epclusa), etc.). Glecaprevir/pibrentasvir (Mavyret) was FDA approved to treat acute hepatitis C virus (HCV) infections in adults and children aged three years and older without cirrhosis or with compensated cirrhosis in June 2025. The AASLD guidelines also note that pre-exposure or post-exposure prophylaxis with antiviral therapy is not recommended. The guidelines have not been updated to include recommendations for glecaprevir/pibrentasvir (Mavyret) in the acute HCV space.
- II. Glecaprevir/pibrentasvir (Mavyret) was studied in a single-arm Phase 3 trial. Participants included were treatment naïve and 12 years and older with confirmed acute HCV infection. Acute HCV infection was defined by a negative anti-HCV antibody, HCV RNA and/or HCV core antigen followed by a positive HCV RNA or HCV core antigen (negative to positive test) or clinical signs and symptoms compatible with acute hepatitis (ALT >5x ULN). Participants with liver decompensated cirrhosis were not included. Participants received glecaprevir/pibrentasvir (Mavyret) 300mg-120mg orally once daily for 8 weeks and followed for 12 weeks. The primary endpoint of sustained virological response at 12 weeks (SVR12) occurred in 96% of the participants (275/286). There were no reported virologic failures or post-treatment relapse.
- III. The overall safety profile in these subjects was similar to that observed in subjects with chronic HCV infection. Serious adverse reactions and/or adverse reactions leading to treatment discontinuation were not observed. The most reported adverse reactions were fatigue (3%), asthenia (2%), headache (2%) and diarrhea (2%).
- IV. The clinical trial has significant limitations that include potential performance bias due to the single arm and open label study design. Sustained virological response at 12 weeks (SVR12) is a surrogate marker and does not directly measure clinical outcomes. However, In the acute setting, many patients are asymptomatic or show nonspecific symptoms that frequently are not

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recognized as being associated with acute HCV infection. At this stage, SVR12 may provide clinical value in prevention of progression to chronic disease and further complications.

References

1. Olysio [Prescribing Information]. Titusville, NJ: Janssen Pharmaceuticals; November 2013.
2. Sovaldi [Prescribing Information]. Foster City, CA: Gilead Sciences; December 2013.
3. Harvoni [Prescribing Information]. Foster City, CA: Gilead Sciences; October 2014.
4. Viekira Pak [Prescribing Information]. North Chicago, IL: Abbvie Inc.; December 2014.
5. Technivie [Prescribing Information]. North Chicago, IL: Abbvie Inc.; July 2015.
6. Daklinza [Prescribing Information]. Princeton, NJ: Bristol Myers Squibb; July 2015.
7. Zepatier [Prescribing Information]. Whitehouse Station, NJ; March 2016.
8. Epclusa [Prescribing Information]. Foster City, CA: Gilead Sciences; June 2016.
9. Mavyret [Prescribing Information]. North Chicago, IL: AbbVie. August 2017.
10. Vosevi [Prescribing Information]. Foster City, CA: Gilead Sciences; July 2017.
11. Boursier J, de Ledinghen V, Zarski JP, Fouchard-Hubert I, Gallois Y, Oberti F, et al: Comparison of Eight Diagnostic Algorithms for Liver Fibrosis in Hepatitis C: New Algorithms Are More Precise and Entirely Noninvasive. *Hepatology* 2012; 55(1): 58-67.
12. Guidance from the American Association for the Study of Liver Diseases (AASLD) and the Infectious Disease Society of America (IDSA) Recommendations for Testing, Managing, and Treating hepatitis C. Available online at <http://www.hcvguidelines.org/full-report-view>.
13. Center for Disease Control Website <http://www.cdc.gov/hepatitis/HCV/HCVfaq.htm#section1>. Accessed 8/1/15.
14. Center for Disease Control Website <http://www.cdc.gov/knowmorehepatitis/timeline.htm>. Accessed 8/17/16
15. Guidance from the American Association for the Study of Liver Diseases (AASLD) and the Infectious Disease Society of America (IDSA) Recommendations for Testing, Managing, and Treating hepatitis C. Available online at <http://www.hcvguidelines.org/full-report-view> Accessed July 28, 2016.
16. A Study to Evaluate Adverse Events and Change in Disease Activity in Adult and Adolescent Participants With Acute Hepatitis C Virus (HCV) Infection on Treatment With Oral Tablets of Glecaprevir (GLE)/Pibrentasvir (PIB). ClinicalTrials.gov identifier: NCT04903626. Available at: <https://www.clinicaltrials.gov/study/NCT04903626?term=NCT04903626&rank=1>.
17. Bhattacharya D, Aronsohn A, Price J, Lo Re V; AASLD-IDSA HCV Guidance Panel. Hepatitis C Guidance 2023 Update: AASLD-IDSA Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. *Clin Infect Dis*.

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated QL table to reflect Mavyret's new approval in acute HCV and updated supporting evidence and appendix.	10/2025
Removed PA edit of Mavyret and added box to state removal has been done; removed Mavyret specific criteria; added criteria requiring rationale why preferred product Mavyret is not appropriate	01/2022
Review of age expansion for Mavyret and Epclusa, no policy update needed	07/2021
Updated to include specific scenarios for Vosevi approval	06/2021
Appendix updated to follow Mavyret label update indicating an 8-week treatment duration in treatment naïve, compensated cirrhosis patients. Add newly available lower doses of Solvaldi and Harvoni.	10/2019
Updated to remove provider specialty and FO requirements	06/10/2019
Updated preferred products to only include Mavyret, sofosbuvir/velpatasvir (authorized generic to Epclusa), and Vosevi.	04/01/2019
Previous reviews	04/2015 11/2014 11/2015 12/2015 04/2016 06/2016 08/2016 09/2016 06/2017 11/2017

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	02/2018
Policy created	02/2014

Appendix 1:

Please note, Mavyret, ledipasvir/sofosbuvir (authorized generic to Harvoni), sofosbuvir/velpatasvir (authorized generic to Epclusa) are the preferred agents for commercial groups.

ACUTE treatment	
Treatment naïve	Mavyret x 8 weeks
CHRONIC treatment	
Genotype 1	
Treatment naïve + No cirrhosis	Mavyret x 8 weeks
	ledipasvir/sofosbuvir (authorized generic to Harvoni) x 8 weeks (HCV RNA < 6 million IU/mL)
	ledipasvir/sofosbuvir (authorized generic to Harvoni) x 12 weeks (HCV RNA ≥ 6 million IU/mL)
	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks
	Other:
Treatment naïve + cirrhosis	Mavyret x 8 weeks
	ledipasvir/sofosbuvir (authorized generic to Harvoni) x 12 weeks
	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks
	Other:
Treatment experienced [^] + No cirrhosis	Mavyret x 16 weeks
	Vosevi x 12 weeks
	Other:
Treatment experienced [^] + cirrhosis	Mavyret x 16 weeks
	Vosevi x 12 weeks
	Other:
Treatment experienced [‡] + No cirrhosis	Mavyret x 12 weeks
	Vosevi x 12 weeks *Genotype 1a ONLY*
	ledipasvir/sofosbuvir (authorized generic to Harvoni) x 12 weeks
	Other:
Treatment experienced [‡] + cirrhosis	Mavyret x 12 weeks
	Vosevi x 12 weeks *Genotype 1a ONLY*
	ledipasvir/sofosbuvir (authorized generic to Harvoni) x 24 weeks
	Other:
Treatment experienced [!] + No cirrhosis	Mavyret x 8 weeks
	Vosevi x 12 weeks *Genotype 1a ONLY*
	Other:
Treatment experienced [!] + cirrhosis	Mavyret x 12 weeks

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	Vosevi x 12 weeks *Genotype 1a ONLY*
	ledipasvir/sofosbuvir (authorized generic to Harvoni) x 24 weeks
	Other:
Genotype 2	
Treatment naïve + No cirrhosis	Mavyret x 8 weeks
	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks
	Other:
Treatment naïve + Cirrhosis	Mavyret x 8 weeks
	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks
	Other:
Treatment experienced^ + No cirrhosis	Vosevi x 12 weeks
	Other:
Treatment experienced^ + Cirrhosis	Vosevi x 12 weeks
	Other:
	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks
	Other:
	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks
	Other:
Treatment experienced [†] + No cirrhosis	Mavyret x 8 weeks
	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks
	Other:
Treatment experienced [†] + Cirrhosis	Mavyret x 12 weeks
	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks
	Other:
Genotype 3	
Treatment naïve + No cirrhosis	Mavyret x 8 weeks
	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks
	Other:
Treatment naïve + Cirrhosis	Mavyret x 8 weeks
	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks
	Other:
Treatment experienced^+ No cirrhosis	Vosevi x 12 weeks
	Other:
Treatment experienced^ + cirrhosis	Vosevi x 12 weeks
	Other:
Treatment experienced [‡] + No cirrhosis	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks

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	Vosevi x 12 weeks
	Other:
Treatment experienced [‡] + cirrhosis	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks
	Vosevi x 12 weeks
	Other:
	Mavyret x 16 weeks
Treatment experienced [†] + No cirrhosis	Vosevi x 12 weeks
	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks
	Other:
	Mavyret x 16 weeks
Treatment experienced [†] + Cirrhosis	Vosevi x 12 weeks
	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks
	Other:
Genotype 4	
Treatment naïve + No cirrhosis	Mavyret x 8 weeks
	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks
	ledipasvir/sofosbuvir (authorized generic to Harvoni) x 12 weeks
	Other:
Treatment naïve + Cirrhosis	Mavyret x 8 weeks
	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks
	ledipasvir/sofosbuvir (authorized generic to Harvoni) x 12 weeks
	Other:
Treatment experienced [^] + No cirrhosis	Vosevi x 12 weeks
	Other:
Treatment experienced [^] + cirrhosis	Vosevi x 12 weeks
	Other:
Treatment experienced [‡] + No cirrhosis	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks
	ledipasvir/sofosbuvir (authorized generic to Harvoni) x 12 weeks
	Other:
	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks
Treatment experienced [‡] + Cirrhosis	ledipasvir/sofosbuvir (authorized generic to Harvoni) x 12 weeks
	Other:
Treatment experienced [†] + No cirrhosis	Mavyret x 8 weeks
	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks

	ledipasvir/sofosbuvir (authorized generic to Harvoni) x 12 weeks
	Other:
Treatment experienced [†] + Cirrhosis	Mavyret x 12 weeks
	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks
	ledipasvir/sofosbuvir (authorized generic to Harvoni) x 12 weeks
	Other:
Genotype 5	
Treatment naïve + No cirrhosis	Mavyret x 8 weeks
	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks
	ledipasvir/sofosbuvir (authorized generic to Harvoni) x 12 weeks
	Other:
Treatment naïve + Cirrhosis	Mavyret x 8 weeks
	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks
	ledipasvir/sofosbuvir (authorized generic to Harvoni) x 12 weeks
	Other:
Treatment experienced [^] + No cirrhosis	Vosevi x 12 weeks
	Other:
Treatment experienced [^] + cirrhosis	Vosevi x 12 weeks
	Other:
Treatment experienced [‡] + No cirrhosis	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks
	ledipasvir/sofosbuvir (authorized generic to Harvoni) x 12 weeks
	Other:
Treatment experienced [‡] + Cirrhosis	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks
	ledipasvir/sofosbuvir (authorized generic to Harvoni) x 12 weeks
	Other:
Treatment experienced [†] + No cirrhosis	Mavyret x 8 weeks
	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks
	ledipasvir/sofosbuvir (authorized generic to Harvoni) x 12 weeks
	Other:
Treatment experienced [†] + Cirrhosis	Mavyret x 12 weeks
	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks
	ledipasvir/sofosbuvir (authorized generic to Harvoni) x 12 weeks

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	Other:
Genotype 6	
Treatment naïve + No cirrhosis	Mavyret x 8 weeks sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks ledipasvir/sofosbuvir (authorized generic to Harvoni) x 12 weeks Other:
Treatment naïve + Cirrhosis	Mavyret x 8 weeks sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks ledipasvir/sofosbuvir (authorized generic to Harvoni) x 12 weeks Other:
Treatment experienced [^] + No cirrhosis	Vosevi x 12 weeks Other:
Treatment experienced [^] + cirrhosis	Vosevi x 12 weeks Other:
Treatment experienced [‡] + No cirrhosis	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks ledipasvir/sofosbuvir (authorized generic to Harvoni) x 12 weeks Other:
Treatment experienced [‡] + Cirrhosis	sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks ledipasvir/sofosbuvir (authorized generic to Harvoni) x 12 weeks Other:
Treatment experienced [†] + No cirrhosis	Mavyret x 8 weeks sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks ledipasvir/sofosbuvir (authorized generic to Harvoni) x 12 weeks Other:
Treatment experienced [†] + Cirrhosis	Mavyret x 12 weeks sofosbuvir/velpatasvir (authorized generic to Epclusa) x 12 weeks ledipasvir/sofosbuvir (authorized generic to Harvoni) x 12 weeks Other:

[^]Treatment experienced after only NS5A (ledipasvir, velpatasvir, daclatasvir, elbasvir, ombitasvir) containing regimen

[‡]Treatment experienced after only NS3/4A PI (simeprevir, boceprevir, telaprevir) containing regimen

[†]Treatment experienced after peginterferon/ribavirin containing regimen with or without sofosbuvir

^{**}Payment consideration for Daklinza with Sovaldi is reserved for no more than a 12 week course of treatment

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP075

Description

C1 esterase inhibitors (Cinryze, Haegarda, Berinert, Ruconest) are injectable medications that regulate the activation of various systems that are thought to modulate the increased vascular permeability during HAE attacks by preventing the generation of bradykinin.

Lanadelumab (Takhzyro), icatibant (Firazyr), icatibant (Sajazir), and berotralstat (Orladeyo) are kallikrein inhibitors. Garadacimab (Andembry) is a recombinant monoclonal antibody targeting activated FXII. Lanadelumab (Takhzyro), icatibant (Firazyr), icatibant (Sajazir), and garadacimab (Andembry) are injectable medications, and berotralstat (Orladeyo) is orally administered.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
C1 esterase inhibitor (Cinryze)	HAE prophylaxis	500 U single use vial for IV administration	20 vials/30 days
C1 esterase inhibitor (Haegarda)		2000 U single use vial for SQ administration	Weight based 60 IU/kg twice weekly, refer to chart below for quantity
		3000 U single use vial for SQ administration	
lanadelumab (Takhzyro)		300 mg/2 mL single dose vial for SQ administration	4 mL/28 days
		300 mg/2 mL prefilled syringe for SQ administration	2 syringes/28 day
		150 mg/mL prefilled syringe for SQ administration*	<u>Ages 2 – 5:</u> 1 syringe/28 day <u>Ages 6 – 12:</u> 2 syringes/28 day
		berotralstat (Orladeyo)	110 mg capsules
150 mg capsules			
garadacimab (Andembry)		200 mg/1.2 mL prefilled syringe	First month: 2.4mL (200 mg)/ 28 days Maintenance: 1.2mL (200 mg) syringe/ 28 days
C1 esterase inhibitor (Berinert)		500 U single use vial for IV administration	Weight based 20 IU/kg, refer to chart below
C1 esterase inhibitor (Ruconest)		2100 U single use vial for IV administration	16 vials/30 days
icatibant (Firazyr)		30 mg/3 mL SQ prefilled syringe	9 syringes (27 mL)/30 days

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icatibant (generic Firazyr)	Treatment of acute	30 mg/3 mL SQ prefilled syringe	9 syringes (27 mL)/30 days
icatibant (Sajazir)	HAE attacks	30 mg/3 mL SQ prefilled syringe	9 syringes (27 mL)/30 days

Initial Evaluation (All information must be supported by documentation and chart notes)

- I. **Medications used for hereditary angioedema (HAE)** may be considered medically necessary when the following criteria below are met and supported by recent chart notes (within the past 12 months):
 - A. Prescribed by, or in consultation with, one of the following specialists: allergist, immunologist, dermatologist, hematologist, pulmonologist, medical geneticist; **AND**
 - B. A diagnosis of **hereditary angioedema (HAE)** indicated by one of the following:
 1. **Type 1 hereditary angioedema (HAE)**: confirmed by documentation of the following laboratory values:
 - i. C1 inhibitor (C1-INH) antigenic level below the lower limit of normal; **AND**
 - ii. C4 level below the lower limit of normal; **AND**
 - iii. C1-INH functional level below the lower limit of normal; **AND**
 - iv. Patient has a family history of hereditary angioedema (HAE); **OR**
 - a. Acquired angioedema has been ruled out (i.e., patient onset of symptoms occurred prior to 30 years of age, normal C1q levels, member does not have underlying disease such as lymphoma or benign monoclonal gammopathy [MGUS], etc.); **OR**
 2. **Type 2 hereditary angioedema (HAE)**: confirmed by documentation of the following laboratory values:
 - i. Normal to elevated C1-INH antigenic level; **AND**
 - ii. C4 level below the lower limit of normal; **AND**
 - iii. C1-INH functional level below the lower limit of normal; **AND**
 - C. The member has been evaluated for potentially treatable triggers of hereditary angioedema (HAE) attacks and is being managed to avoid triggers; **AND**
 1. **For prophylactic treatment of hereditary angioedema (HAE)**:
 - i. C1 esterase inhibitor (Cinryze and Haegarda), lanadelumab (Takhzyro), berotralstat (Orladeyo) or garadacimab (Andembry) is requested; **AND**
 - a. The member is not prescribed more than one agent FDA-approved for hereditary angioedema (HAE) prophylaxis (e.g., C1 esterase inhibitor (Cinryze and Haegarda), lanadelumab (Takhzyro), berotralstat (Orladeyo), garadacimab (Andembry)); **AND**
 - b. The member has a history of at least one of the following criteria for hereditary angioedema (HAE) prophylaxis:
 - i. History of ≥ 2 severe hereditary angioedema (HAE) attacks per month (e.g., airway swelling, debilitating cutaneous or gastrointestinal complications) that required “on-demand” therapy (e.g., icatibant [Firazyr], icatibant [Sajazir], Berinert, Ruconest, Kalbitor)
 - ii. The member is disabled ≥ 5 days per month by hereditary angioedema (HAE)

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- iii. The member has a history of hereditary angioedema (HAE) laryngeal attacks; **AND**
 - c. The member is ≥ 2 years to < 6 years of age; **AND**
 - i. The request is for lanadelumab (Takhzyro) 150 mg/mL prefilled syringe; **OR**
 - d. The member is ≥ 6 years of age; **AND**
 - i. The request is for C1 esterase inhibitor (Cinryze); **OR**
 - ii. The request is for lanadelumab (Takhzyro); **OR**
 - iii. The request is for C1 esterase inhibitor (Haegarda); **AND**
 - 1. Member's current weight within the last six months has been documented to dose appropriately; **OR**
 - e. The member is ≥ 12 years of age; **AND**
 - i. The request is for lanadelumab (Takhzyro), berotralstat (Orladeyo), C1 esterase inhibitor (Cinryze), or garadacimab (Andembry); **OR**
 - ii. The request is for C1 esterase inhibitor (Haegarda); **AND**
 - 1. Member's current weight within the last six months has been documented to dose appropriately; **OR**
- 2. **For acute treatment of hereditary angioedema (HAE) attacks;**
 - i. Icatibant (Firazyr), icatibant (Sajazir), OR C1 esterase inhibitor (Berinert, Ruconest) is requested; **AND**
 - ii. The member is NOT prescribed more than one agent FDA-approved for hereditary angioedema (HAE) acute treatment (e.g., icatibant [Firazyr], icatibant [Sajazir], C1 esterase inhibitor (Berinert, Ruconest), ecallantide (Kalbitor); **AND**
 - iii. The member has a history of attacks that induce significant burden of disease or impact to activities of daily living due to hereditary angioedema (HAE) (e.g., impairment in work performance/productivity, facial swelling, painful distortion of the affected area, laryngeal attacks or airway swelling, severe gastrointestinal complications); **AND**
 - iv. **For C1 esterase inhibitor (Berinert):** the member is ≥ 6 years of age; **AND**
 - a. Documentation of current weight within the last six months, to dose appropriately; **OR**
 - v. **For C1 esterase inhibitor (Ruconest):** the member is ≥ 13 years of age; **AND**
 - a. Treatment with C1 esterase inhibitor (Berinert) AND generic icatibant/icatibant (Sajazir), have been ineffective, contraindicated, or not tolerated; **OR**
 - vi. **For generic icatibant (Firazyr):** the member is ≥ 18 years of age; **OR**
 - vii. **For icatibant (Sajazir):** the member is ≥ 18 years of age; **AND**
 - a. Generic icatibant has been ineffective, not tolerated, or contraindicated; **OR**

- viii. **For icaltiban (Firazyr):** the member is ≥ 18 years of age; **AND**
 - a. Generic icaltiban has been ineffective, not tolerated, or contraindicated; **AND**
 - b. Icaltiban (Sajazir) has been ineffective, not tolerated, or is contraindicated.
- II. Medications used for hereditary angioedema (HAE) are considered investigational when used for all other conditions or scenarios, including but not limited to:
 - A. Combination use of acute therapies (e.g., icaltiban [Firazyr], C1 esterase inhibitor [Ruconest, Berinert], ecallantide [Kalbitor], icaltiban [Sajazir])
 - B. Combination use of prophylactic therapies (i.e., C1 esterase inhibitor (Cinryze and Haegarda), lanadelumab (Takhzyro), berotralstat (Orladeyo), garadacimab (Andembry))
 - C. Angioedema due to other causes (e.g., hereditary angioedema (HAE) with normal C1 inhibitor levels, medication induced, sepsis, cardiovascular comorbidities or conditions, allergic reaction, etc.)

Renewal Evaluation (All information must be supported by documentation and chart notes)

- 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 continues to be evaluated for potentially treatable triggers of hereditary angioedema (HAE) attacks and is being managed to avoid triggers; **AND**
- IV. The member has been seen and evaluated for medication efficacy and safety in the past 12 months; **AND**
- V. The quantity of medication prescribed does not exceed that needed to treat or prevent current average number of attacks or expected number of attacks; **AND**
- VI. Documentation the member has experienced functional improvement AND improvement in the number, severity, or duration of attacks; **AND**
- VII. **For prophylactic treatment of hereditary angioedema (HAE):**
 - A. The member has not been prescribed more than one medication FDA-approved for hereditary angioedema (HAE) prophylaxis (i.e., C1 esterase inhibitor (Cinryze and Haegarda), lanadelumab (Takhzyro), berotralstat (Orladeyo), garadacimab (Andembry)); **AND**
 - B. **For C1 esterase inhibitor (Haegarda):** documentation of current weight (within the last three months, to calculate appropriate dose); **OR**
 - C. **For lanadelumab (Takhzyro):** one of the following is met:
 - i. The member has been free of acute attacks for ≥ 6 months; **AND**
 - a. The dosing frequency for Takhzyro will be reduced to every 4 weeks (e.g., 150 mg/mL every 4 weeks, 300 mg/2 mL every 4 weeks) [Note: Dose reductions may not apply to members >2 years to <6 years of age]; **OR**
 - ii. The member has had acute attack(s) in the past 6 months; **AND**

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- a. Rationale for medical necessity is provided for maintaining the dose at 'every two weeks' dosing interval; **OR**
 - D. **For C1 esterase inhibitor (Cinryze):**
 - i. Documentation of current weight; **AND**
 - ii. Dosage will not exceed 80 International Units (IU)/kg body weight; **OR**
 - E. The request is for **berotralstat (Orladeyo)**, or **garadacimab (Andembry)**; **OR**
- VIII. **For acute treatment of hereditary angioedema (HAE) attacks:**
 - A. The member has not been prescribed more than one medication FDA approved for HAE treatment (e.g., icatibant [Firazyr], icatibant [Sajazir], C1 esterase inhibitor (Berinert, Ruconest), ecallantide (Kalbitor)); **AND**
 - B. **For icatibant (Firazyr):** the member has tried and failed, not tolerated, or has contraindication to generic icatibant AND icatibant (Sajazir); **OR**
 - C. **For icatibant (Sajazir):** the member has tried and failed, not tolerated, or has contraindication to generic icatibant
 - D. **For C1 esterase inhibitor (Berinert):** documentation of current weight within the last three months, to calculate appropriate dose

Supporting Evidence

- I. Hereditary angioedema (HAE) is a rare disease characterized by recurrent and sometimes severe episodes of angioedema without urticarial or pruritus. Skin and mucosal tissues in the upper respiratory and gastrointestinal tracks are often affected and may have airway involvement leading to asphyxiation if not treated appropriately. It should be noted that it is not uncommon for patients to have mild and/or self-limiting attacks that do not require treatment. Non-pharmacologic and pharmacologic management of HAE is very complex and requires confirmatory tests and monitoring by, or in close consultation with, a specialist.
- II. Hereditary angioedema (HAE) is divided into two broad categories: HAE due to C1INH deficiency (HAE-C1INH) and HAE with normal C1INH (HAE-nl-C1INH). Hereditary angioedema (HAE)-C1INH is further subdivided into type 1 and type 2, which appear to be clinically similar. Hereditary angioedema (HAE)-nl-C1INH HAE was previously called type 3 HAE, however the "type 3" term has become obsolete. Hereditary angioedema (HAE)-nl-C1INH HAE is further subdivided based on the underlying mutation or unknown in cases where the mutation has not been found. Clinical trials have only evaluated HAE therapies in patients with HAE-C1INH (types 1-2). There is insufficient data available due to the lack of high or moderate quality data to determine the efficacy of C1 esterase inhibitor, human (Cinryze), C1 esterase inhibitor, human (Haegarda), berotralstat (Orladeyo), lanadelumab-flyo (Takhzyro), and garadacimab in prevention of HAE attacks in patients with HAE-nl-C1INH at this time.
- III. Normal C1-INH levels are generally 18-37 mg/dL, normal C4 levels are generally 10-40 mg/dL, normal functional level C1-INH is >67%, normal C1q levels are generally 5-8.6 mg/dL.
- IV. Evaluation, documentation, and patient understanding of triggers is essential in the management of HAE and can reduce the number of disabling attacks and medication requirements. The most common triggers include stress, NSAIDS, ACE inhibitors, antibiotics, trauma, illness, dental work, hormonal fluctuations, and food sensitivities, although there are many other patient specific triggers. Furthermore, allergic/anaphylactic reactions and adverse effects related to foods and medications should be ruled out in light of an HAE diagnosis.
- V. Hereditary angioedema treatment modalities include acute management and prophylactic methods. Acute therapies, also known as "on-demand" therapy, is essential in serious,

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- debilitating, and laryngeal attacks, options include C1 esterase inhibitors (Berinert, Ruconest), bradykinin antagonist (icatibant [Firazyr], icatibant [Sajazir] – available generic), and kallikrein inhibitor (Kalbitor). Only one of these therapies should be prescribed and used at one time.
- VI. Generic icatibant and icatibant (Sajazir) are both available AP rated (therapeutically equivalent) generics to icatibant (Firazyr).
 - VII. In addition to treating attacks of angioedema, patients with HAE may require prophylactic treatment. The goal of prophylactic treatment is either to reduce the likelihood of swelling in a patient undergoing a stressor or procedure likely to precipitate an attack (short-term prophylaxis) or to decrease the overall number, severity, and burden of angioedema attacks per 2020 United States Hereditary Angioedema Association Medical Advisory Board (HAEA MAB) Guidelines for the Management of Hereditary Angioedema and the 2021 International World Allergy Organization (WAO)/ European Academy of Allergy and Clinical Immunology (EAACI) Guideline for the Management of Hereditary Angioedema.
 - VIII. Prophylactic therapy should be considered based on the number of attacks, severity of the attacks, comorbid conditions, emergency department visits, inadequate response or control using acute treatments, and/or where severe, debilitating, or laryngeal attacks are recurrent. Trauma or stress-related events, such as surgeries or dental procedures may entail the need for a short-term prophylaxis therapy. Current 2020 US HAEA MAB guidelines recommend the use of a single dose of plasma derived C1 inhibitor (pdC1INH; e.g., Berinert) as the preferred agent for short-term prophylaxis or a course of anabolic androgen (e.g., danazol) when access to Berinert is limited.
 - IX. For long-term HAE prophylaxis, the 2020 USA HAEA MAB/2021 WAO/EAACI guidelines recommend the use of IV or SQ replacement of pdC1INH as the first-line agents (e.g, Cinryze, Haegarda) along with kallikrein inhibitors (e.g., Takhzyro, Orladeyo). Before the advent of current HAE prophylactic agents, androgens (danazol), antifibrinolytics (aminocaproic acid, tranexamic acid) were used in practice for HAE prophylaxis based on their mechanisms of action and limited clinical trials (1970s and 1980s) indicating symptomatic benefits. However, the current HAEA MAB guidelines recommend these agents as second-line therapies. Use of the second-line prophylactic agents should be reserved for when first-line therapies are not available. Lack of strong clinical data coupled with significant risks of long-term adverse reactions, and lack of FDA approval in the setting of HAE prophylaxis has driven this change in practice in recent years. It should be noted that only danazol is approved in the US for HAE prophylaxis. However, dose-related side effects, considerations on populations to avoid use in (age <16, pregnant and breastfeeding women), and tolerability concerns limit its widespread use.
 - X. Patients with HAE may also require short-term prophylactic treatment to reduce the likelihood of swelling in a patient before an invasive medical, surgical or dental procedure that is likely to precipitate in an attack. Either plasma-derived C1-inhibitor (pdC1INH) or a course of anabolic androgen is administered for short-term prophylaxis of HAE. The medications in this policy are not specifically FDA-approved for use in short-term prophylaxis at this time.
 - XI. Both on-demand and prophylactic HAE therapies have FDA-approvals for various age groups; therefore, the ages outlined in this policy are based on FDA-approval. Of note, pediatric populations are underrepresented in clinical trials; however, FDA-approval is often based on clinical experience from a few pediatric patients coupled with several years of safety data in other age populations with limited available treatment options for a potentially life-threatening condition.
 - XII. Lanadelumab (Takhzyro) was evaluated in two Phase 3 studies in patients aged 12 years and older with HAE.

- Study DX2930-03 was a Phase 3, multicenter, randomized, double-blind, placebo-controlled parallel-group study. The 26-week study included 125 patients 12 years of age and older with HAE-I or HAE-II who experienced at least one investigator-confirmed attack per 4 weeks during the run-in period. During the study run-in period, attack rates of ≥ 3 attacks/month were observed in 52% of patients. The primary endpoint was mean monthly attack rate from day 0 to 182, those in the Takhzyro 150 mg every 4 weeks arm had 0.48 mean monthly attack rate, those in the Takhzyro 300 mg every 4 weeks arm had 0.53 mean monthly attack rate and 0.26 mean monthly attack rate was observed in those who received Takhzyro 300 mg every 2 weeks, while those in the placebo arm had a 1.97 mean monthly attack rate ($p < 0.001$). This secondary endpoint of the study was mean number of monthly attacks requiring acute treatment from day 0 to 182. Clinically meaningful and statistically significant outcomes were observed across all Takhzyro arms. Participants in the placebo arm had a mean of 1.64 monthly attacks requiring acute treatment, compared to 0.31 (150 mg every 4 weeks), 0.42 (300 mg every 4 weeks) and 0.21 (300 mg every 2 weeks) [$p < 0.001$] as observed across all Takhzyro arms.
- The open-label Phase 3 extension study DX2930-04 evaluated the long-term safety of lanadelumab 300 mg Q2W in Types I and II HAE patients. The study consisted of rollover subjects who completed the double-blind treatment period of Trial DX2930-03 and non-rollover subjects who enrolled directly into the OLE study. A secondary objective of the study was to characterize the outer bounds of dosing frequency in the rollover subjects. The primary objective of the study was to provide long-term safety data which include adverse events/serious adverse events, clinical labs (hematology, chemistry, LFTs, UA, coagulation, pregnancy), ECG, vital signs, physical exam, and ADA testing.
- An open-label, single-arm, Phase 3 trial (SPRING) measured safety, pharmacokinetics and pharmacodynamics (PK/PD) of lanadelumab (Takhzyro) in patients ≥ 2 years to 12 years of age (N=21) consisting of 17 participants in the 6 years to 12 years age group (group A) and 4 participants aged 2 years to 6 years of age (group B). At 52 weeks of treatment exposure, lanadelumab (Takhzyro) exhibited comparable PK/PD characteristics in pediatric patients (group A) to those for systemic drug exposure in adult patients. For group B patients (<6 years of age), the minimum steady-state plasma drug levels were 50% to 60% lower than those for adult patients (reported from previous clinical data), however were reported to produce a treatment response. During the SPRING trial, 76% (n=16) participants remained HAE attack-free during full treatment period and the rate of HAE attacks per month reduced by 94% versus baseline (1.84 attacks per month to 0.08 attacks). Although robust conclusions may not be drawn from this data due to open-label study design, limited sample size and lack of comparator, this data provides support to previously reported efficacy of lanadelumab (Takhzyro) in patients >12 years of age. Additionally, no additional safety signals were reported during SPRING trial. Thirty-three percent of participants reported injection site reactions as the common AE, which did not lead to treatment interruptions, discontinuations or hospitalizations.

XIII. Berotralstat (Orladeyo) was evaluated in a three-part Phase 3 study, and the approval was based on data submitted from part 1 (24 weeks).

- APeX-2 (part 1) was a double-blind, randomized, placebo-controlled trial in 121 patients with type I or type II HAE. The primary efficacy outcome of part one was

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the rate of investigator confirmed HAE attacks per month at week 24, which was 1.31 ($p < 0.001$) for the berotralstat 150 mg arm, 1.65 ($p = 0.024$) for the berotralstat 110 mg arm and 2.35 for placebo. Although berotralstat (Orladeyo) met its primary efficacy endpoint, the study failed to meet statistical significance in its secondary endpoint, which was the change from baseline of AE-QOL total scores at 24 weeks. The long-term efficacy and safety of this product is currently unknown due to the lack of published long-term data. The distribution of on-demand medication use during the study across all study arms was not provided; therefore, there is a risk the concomitant therapies confounded the outcome results.

- APeX-2 (part 2) was 24-week, Phase 3, double-blinded, placebo-controlled trial. Participants ≥ 12 years, with a confirmed diagnosis of HAE1/2, and at least one attack per month were included. A total of 108 participants were evaluated. Participants from APeX-2 part 1 were to continue berotralstat (Orladeyo) 110mg or 150mg. Participants previously on placebo or new to the study were randomized to start berotralstat (Orladeyo) 110mg or 150mg. Baseline characteristics were similar, mean age of 41.6 years, mostly female and white and the mean baseline number of HAE attack was 3. The mean number of HAE attacks was 1.35 in the group that was previously on berotralstat (Orladeyo) 110mg and continued this dose, 1.06 in the initial 150mg group and continued this dose, 1.25 in the placebo-to-110mg group, and 0.57 in the placebo-to-150mg group.

XIV. Garadacimab is a recombinant monoclonal antibody targeting activated FXII. Garadacimab was evaluated in a Phase 3, double-blinded, placebo-controlled randomized trial. Participants ≥ 12 years, with a confirmed diagnosis of HAE1/2, and at least one attack per month were randomized to receive subcutaneous (SC) garadacimab 400mg loading dose and 200mg every month or placebo. Participants were able to use any on-demand-therapy throughout the trial and those with HAE-nl-C1INH were not permitted. Baseline characteristics were similar between both groups (total $N = 65$) with a mean age of 38 years, mostly female and white. The mean HAE attack per month was 3.1 in the garadacimab group and 2.5 in the placebo group. The trial demonstrated that the mean number of investigator-confirmed HAE attacks per month was significantly lower in the garadacimab group (0.27; 95% CI 0.05-0.49) than in the placebo group (2.01; 1.44-2.57; $p < 0.0001$). The change in reduction in HAE attacks per month compared to placebo was -89% (95% CI, -96 to -76), $P < 0.0001$. Common adverse events included upper respiratory tract infection, nasopharyngitis, and headaches.

- A 12-month open label extension trial demonstrated that participants ≥ 12 years, with a confirmed diagnosis of HAE1/2, and at least one attack per month on garadacimab 200mg SC once monthly had a mean of 0.16 HAE attacks per month with a 95% reduction from baseline (95%CI, 92.8-96.5).

XV. There are no direct head-to-head studies comparing lanadelumab (Takhzyro) and berotralstat (Orladeyo) to establish superior safety or efficacy of one product over the other; however, lanadelumab (Takhzyro) has a more established safety profile, and favorable quality of evidence for efficacy.

Investigational or Not Medically Necessary Uses

- I. Use of two or more therapies for the same indication (e.g., acute or prophylactic) has not been evaluated for safety and efficacy.
- II. The medications listed in this policy have not been sufficiently evaluated for safety and efficacy outside of hereditary angioedema.

Appendix

Weight-based dosing for Haegarda and Berinert

Medication	Body Weight (kg)	Vial Configuration	Vials per Dose	Number of Vials per 30 days
Haegarda	Up to 33 kg	2000 unit	1	8
	34-50	3000 unit	1	8
	51-67	2000 unit	2	16
	68-100	3000 unit	2	16
	101-133	2000 unit	4	32
	134-150	3000 unit	3	32
Berinert	Up to 25	500 unit	1	4
	25 - 50		2	8
	50 - 75		3	12
	75 - 100		4	16
	100-125		5	20
	125-150		6	24

References

1. Takhzyro (lanadelumab-flyo) [prescribing information]. Lexington, MA: Takeda Pharmaceuticals USA; February 2023.
2. Berinert [Prescribing Information]. Kankakee, IL: CSL Behring LLC. July 2016.
3. Haegarda [Prescribing information]. Kankakee, IL: CSL Behring LLC; September 2020.
4. Firazyr [Prescribing Information]. Lexington, MA: Shire Orphan Therapies, LLC. November 2015.
5. Cinryze (C1 inhibitor, human) [prescribing information]. Lexington, MA: Takeda Pharmaceuticals USA Inc; February 2023.
6. Ruconest [Prescribing Information]. Raleigh, NC: Santarus, Inc. February 2015.
7. Kalbitor [Prescribing Information]. Dyax Corporation. Burlington, MA. 2014.
8. Orladeyo (berotralstat) [prescribing information]. Durham, NC: BioCryst Pharmaceuticals Inc; November 2023.
9. Craig T, Aygören-Pürsün EA, Bork K, et al. World Allergy Organization (WAO) guideline for the management of hereditary angioedema. World Allergy Organ J. 2012; 5(12):182-199.
10. Zuraw BL, Banerji A, Bernstein JA, Busse PJ, Christiansen SC, Davis-Lorton M, et al. US Hereditary Angioedema Association Medical Advisory Board 2013 recommendations for the management of hereditary angioedema due to C1 inhibitor deficiency. J Allergy Clin Immunol: In Practice 2013;1:458-67. <http://dx.doi.org/10.1016/j.jaip.2013.07.002>.
11. Bowen et al. 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. Allergy, Asthma & Clinical Immunology. 2010. 6(24):1-13.
12. Aygören-pürsün E, Soteres D, Moldovan D, et al. Preventing Hereditary Angioedema Attacks in Children Using Cinryze Interim Efficacy and Safety Phase 3 Findings. Int Arch Allergy Immunol. 2017;173(2):114-119.
13. Germeis AE., Speletas M. Genetics of hereditary angioedema revisited. Clin Rev Allergy Immunol. 2016;51(2); 170-182.
14. MM, MM, IA, et al. The international WAO/EAACI guideline for the management of hereditary angioedema – the 2017 revision and update. Allergy. 2018;73(8): 1575-1596.
15. U.S. Food and Drug Administration Announcement. Approval of Haegarda for Prevention of Hereditary Angioedema Attacks in Pediatric Patients. Accessed October 2020. Available at: <https://www.cslbehring.com/newsroom/2020/haegarda-pediatric-label-update>
16. BLA 761090 Multi-disciplinary Review and Evaluation of Takhzyro (lanadelumab). Center for Drug Evaluation and Research. 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/761090Orig1s000MultidisciplineR.pdf. Accessed December 17, 2020.
17. Zuraw B, Lumry WR, Johnston DT, et al. Oral once-daily berotralstat for the prevention of hereditary angioedema attacks: a randomized, double-blind, placebo-controlled phase 3 trial, J. Allergy Clin. Immunol (2020), <https://doi.org/10.1016/j.jaci.2020.10.015> (pre-proof)
18. Icatibant Injection. Drug Facts and Comparisons. Facts & Comparisons eAnswers. Wolters Kluwer Health, Inc. Riverwoods, IL. Accessed October 18, 2021. <http://online.factsandcomparisons.com>

19. Maurer M, Lumry WR, Li H, et al. Efficacy and Safety of Lanadelumab in Pediatric Patients Aged 2 to <12 years With Hereditary Angioedema: Results From the Open-Label, Multicenter Phase 3 SPRING Study. Abstract submitted to European Academy of Allergy and Clinical Immunology Hybrid Congress 2022.
20. Craig TJ, Reshef A, Li HH, et al. Efficacy and safety of garadacimab, a factor XIIIa inhibitor for hereditary angioedema prevention (VANGUARD): a global, multicentre, randomised, double-blind, placebo-controlled, phase 3 trial [published correction appears in Lancet. 2023 Apr 15;401(10384):1266. doi: 10.1016/S0140-6736(23)00739-0]. Lancet. 2023;401(10382):1079-1090.
21. Reshef A, Hsu C, Katelaris CH, et al. Long-term safety and efficacy of garadacimab for preventing hereditary angioedema attacks: Phase 3 open-label extension study. Allergy. Published online October 7, 2024.
22. Beard N, Frese M, Smertina E, Mere P, Katelaris C, Mills K. Interventions for the long-term prevention of hereditary angioedema attacks. Cochrane Database Syst Rev. 2022;11(11):CD013403. Published 2022 Nov 3.
23. Maurer M, Magerl M, Betschel S, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-The 2021 revision and update. Allergy. 2022;77(7):1961-1990.
24. Busse PJ, Christiansen SC, Riedl MA, et al. US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema. J Allergy Clin Immunol Pract. 2021;9(1):132-150.e3.

Related Policies

Currently there are no related policies

Policy Implementation/Update:

Action and Summary of Changes	Date
Realigned Takzyro renewal criteria for better flow	09/2025
Updated diagnostic criteria for Type 1 HAE. Added dose verification for Cinryze upon renewal.	08/2025
Added garadacimab (Andembry) to the policy. Updated supporting evidence for berotralstat (Orladeyo) to include findings of APeX-2 part 2 study.	06/2025
Added expanded indication for Takhzyro (>2 years of age); In the prophylaxis setting, removed requirement of trial with danazol, aminocaproic acid, and tranexamic acid following updated guideline recommendations; updated supporting evidence. Removed requirement of specialist prescribing upon renewal. Increased initial approval duration from 3 months to 6 months.	04/2023
Addition of icatibant (Sajazir) to policy, requiring use of generic icatibant prior to use of Sajazir and allowing brand Firazyr coverage only if medical necessity established for brand over generic (generic icatibant and Sajazir)	10/2021
Added Orladeyo criteria for prophylactic treatment of HAE for P&T, added renewal criteria requiring initial policy criteria needs to be met, no continuation based on samples and must have had prior approval by plan.	02/2021
Age for Haegarda expanded down to six years of age (from previous 12)	10/2020
Added age restriction to Takhzyro of ≥ 12 years of age	03/2020
Policy created and criteria added to initial and renewal portions. Takhzyro combined with other agents. Specification on inappropriateness of dual therapy use, medical necessity of therapy, and addition of generic icatibant to the policy and use required prior to brand payment consideration.	10/2019
Takhzyro criteria created for P&T.	10/2018
Criteria updated to include Cinryze prophylactic therapy for patients six years of age and older, a new FDA approved age range.	01/2018
HAE indication review completed, agents included in policy were updated and questions added to align with clinical appropriateness and medical criteria.	11/2017
Criteria created	10/2016

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP127

Description

Human chorionic gonadotropin (hCG) stimulates production of gonadal steroid hormones by causing production of androgen by the testes and the development of secondary sex characteristics in males. In females, hCG acts as a substitute for luteinizing hormone (LH) to stimulate ovulation.

Length of Authorization

- Initial: 12 months (for hypogonadotropic hypogonadism); six months (for cryptorchidism)
 - Renewal: 12 months (for hypogonadotropic hypogonadism)*
- * Other indications are not eligible for renewal

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
human chorionic gonadotropin (human chorionic gonadotropin)	10,000 unit vial	Hypogonadotropic hypogonadism Ovulation induction* Prepubertal cryptorchidism	5 vials/30 days
human chorionic gonadotropin (Novarel)	5,000 unit vial		10 vials/30 days
human chorionic gonadotropin (Pregnyl)	10,000 unit vial		5 vials/30 days

*Drugs used in the treatment of fertility are excluded from coverage. Please refer to the member handbook/certificate of coverage for further information.

Initial Evaluation

- I. Human chorionic gonadotropin (Novarel; Pregnyl) may be considered medically necessary when the following criteria below are met:
 - A. A diagnosis of one of the following:
 1. **Hypogonadotropic hypogonadism; AND**
 - i. Two sub-normal testosterone concentration levels taken on two separate mornings while fasting; **AND**
 - ii. Treatment with all of the following has been ineffective, contraindicated, or not tolerated:
 - a. Generic injectable testosterone (i.e. testosterone cypionate, testosterone enanthate); **AND**
 - b. Generic topical testosterone (i.e. generic testosterone 1% gel); **OR**
 2. **Prepubertal cryptorchidism; AND**
 - i. Not due to anatomical obstruction

- II. Human chorionic gonadotropin (Novarel; Pregnyl) is considered not medically necessary when criteria above are not met and/or when used for:
 - A. Men with low testosterone concentration and without clinical symptoms and signs consistent with testosterone deficiency. The routine assessment of testosterone level in the absence of hypogonadal symptoms is not advised.
 - B. Men with a single, sub-normal testosterone concentration that is not repeatable per the U.S. Endocrine Society.
 - C. Men with symptoms of hypogonadism; however, current testosterone level is within normal range.
- III. Human chorionic gonadotropin (Novarel; Pregnyl) is considered investigational when used for all other conditions including but not limited to:
 - A. Age-related hypogonadism
 - B. Men with type 2 diabetes mellitus with low testosterone for the purpose of improving glycemic control
 - C. 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. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- III. A diagnosis of **hypogonadotropic hypogonadism; AND**
- IV. Member has exhibited improvement or stability of disease symptoms.

Supporting Evidence

- I. Human chorionic gonadotropin (Novarel; Pregnyl) is FDA approved for the treatment of hypogonadotropic hypogonadism, prepubertal cryptorchidism, and ovulation induction. Coverage of medications used in the treatment of fertility is an excluded benefit; thus, criteria for coverage in the setting of ovulation induction is unrepresented within this policy.
- II. There are several dosing regimen options in the setting of prepubertal cryptorchidism; however the label only supports a six week course with the potential of another series given one month later if the initial course was not successful.
- III. Per the 2018 AUA guidelines, diagnosis of hypogonadism should be confirmed prior to initiating testosterone replacement therapy. Testosterone levels should be drawn ideally between 8 and 10 AM while fasting due to the diurnal fluctuation of testosterone and its sensitivity to glucose ingestion. A separate, confirmatory measurement is recommended.
- IV. Thirty percent of men with an initial testosterone concentration in the hypogonadal range can have a measurement within the normal range on repeat measurement.
- V. The Endocrine Society strongly advises against “trial periods” of testosterone in men with a single sub-normal testosterone concentration and vague symptoms of deficiency.

- VI. In patients within normal range, or have low testosterone concentration due to age, obesity or otherwise, the benefit of increased testosterone has not been shown. Rather, in this patient population with low testosterone and an intact gonadal system, increasing testosterone is associated with an increase of certain health risks, including cardiovascular disease. Because of this, the FDA has required manufacturers to label testosterone products warning of the increased risk for heart attack and stroke.

Investigational or Not Medically Necessary Uses

- I. All of the aforementioned conditions listed in the not medically necessary section are considered to be excluded from coverage.
- II. In the conditions listed, there is insufficient information, or, information reports inconclusive evidence, to support the safety and efficacy of using human chorionic gonadotropin (Novarel; Pregnyl).

References

1. Novarel [Prescribing Information]. Parsippany, NJ: Ferring Pharmaceuticals, Inc. May 2018.
2. Pregnyl [Prescribing Information]. Whitehouse Station, NJ: Merck & Co., January 2015.
3. Bhasin S, Brito JP, Cunningham GR, et al. Testosterone Therapy in Men with Hypogonadism: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2018; 103:1715.
4. Yeap B, Wu F. Clinical practice update on testosterone therapy for male hypogonadism: Contrasting perspectives to optimize care. Clinical Endocrinology 2019; 56:65. Available at: DOI: 10.1111/cen.13888
5. Crowley, W. F. (2018, July 23). Approach to patient with delayed puberty. Retrieved from UpToDate.
6. Snyder, P. J. (2018, April 21). Clinical features and diagnosis of male hypogonadism. Retrieved from UpToDate.
7. National Institute on Aging. Scientific task force to examine usefulness of testosterone replacement therapy in older men. NIH News Release. November 6, 2002. Available at: <http://www.nia.nih.gov/NewsAndEvents/PressReleases/PR20021106ScientificTask.htm> (access date April 4, 2007).

Policy Implementation/Update:

Date Created	December 2019
Date Effective	December 2019
Last Updated	December 2019
Last Reviewed	12/2019

Action and Summary of Changes	Date

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP212

Description

Hydrocortisone (Alkindi Sprinkle) is an orally administered corticosteroid.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
hydrocortisone (Alkindi Sprinkle)	0.5mg capsules	Adrenocortical insufficiency	10 mg/m ² /day*
	1mg capsules		
	2mg capsules		
	5mg capsules		

*limited to three capsules a day

Initial Evaluation

- I. **Hydrocortisone (Alkindi Sprinkle)** may be considered medically necessary when the following criteria below are met:
 - A. The member is 17 years of age or younger; **AND**
 - B. The medication is prescribed by, or in consultation with, an endocrinologist; **AND**
 - C. A diagnosis of an **Adrenocortical insufficiency** (e.g. primary adrenal insufficiency, Addison's Disease, secondary adrenal insufficiency) and the following are met:
 1. The request is for hydrocortisone (Alkindi Sprinkle) 0.5 mg, 1 mg, or 2 mg capsules; **AND**
 - i. Each individual dose is less than 5 mg (of note, when a 5 mg dose is reached, member is required to transition to generic hydrocortisone oral tablets, unless contraindicated); **AND**
 - ii. Treatment with hydrocortisone compound formulation (solution or suspension) has been ineffective, contraindicated, or not tolerated; **OR**
 2. The request is for hydrocortisone (Alkindi Sprinkle) 5 mg capsules;
 - i. Treatment with generic hydrocortisone oral tablet is contraindicated (documentation must be attached); **AND**
 - ii. Treatment with hydrocortisone compound formulation (solution or suspension) has been ineffective, contraindicated, or not tolerated
- II. Hydrocortisone (Alkindi Sprinkle) is considered not medically necessary when the following are met:

- A. Total daily dose requirement for hydrocortisone may be met using hydrocortisone (Cortef) oral tablets (5 mg, 10 mg, or 20 mg) or hydrocortisone compound (solution or suspension)
 - B. Treatment requiring hydrocortisone (Alkindi Sprinkle) 5 mg capsules
- III. Hydrocortisone (Alkindi Sprinkle) is considered investigational when used for all other conditions, including but not limited to:
- A. Treatment of members 18 years of age or older, requiring hydrocortisone therapy
 - B. Chemotherapy induced nausea and vomiting

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. The request is for hydrocortisone (Alkindi Sprinkle) 0.5 mg, 1 mg, or 2 mg capsules; **AND**
 - Each individual dose is less than 5 mg (of note, when a 5 mg dose is reached, member is required to transition to generic hydrocortisone oral tablets, unless contraindicated); **AND**
 - Treatment with hydrocortisone compound formulation (solution or suspension) has been ineffective, contraindicated, or not tolerated; **OR**
- IV. The request is for hydrocortisone (Alkindi Sprinkle) 5 mg capsules;
 - Treatment with generic hydrocortisone oral tablet is contraindicated (documentation must be attached); **AND**
 - Treatment with hydrocortisone compound formulation (solution or suspension) has been ineffective, contraindicated, or not tolerated
- V. Provider attests that the member remains ineligible to transition to generic hydrocortisone tablets and compounded hydrocortisone products (solution or suspension); **AND**
- VI. Member has exhibited improvement or stability of disease symptoms (e.g. improved cortisol levels over baseline, improvement in symptoms such as hypotension, hyponatremia)

Supporting Evidence

- I. Hydrocortisone (Alkindi Sprinkles) is a corticosteroid, indicated as a replacement therapy in pediatric patients (less than 17 years of age) with adrenocortical insufficiency. Alkindi Sprinkle is a granular formulation of hydrocortisone, which was designed to overcome the barrier of inaccuracy of dosing (when using currently available hydrocortisone formulations) for younger patients.
- II. Pediatric patients (neonate to <17 years old) usually require less than 5 mg of total daily dose of hydrocortisone. The daily dose of hydrocortisone is usually divided into two to three doses with initial dose of 8mg/m² to 10mg/m² per day. Hydrocortisone (Alkindi Sprinkle) is supplied in a pack size of 50 capsules to be stored in the original bottle (unbreakable package). Quantity limit

- for hydrocortisone (Alkindi Sprinkles) is based on total daily dose divided into two to three individualized doses and should be rounded up to the nearest pack size.
- III. Currently there are no published clinical trial or treatment regimens for children with Primary Adrenal Insufficiency (PAI). The Journal of Endocrinology and Metabolism guideline recommends that treatment in children is aimed at managing and controlling symptoms of adrenal insufficiency with optimal doses that allow for growth and pubertal development. Because PAI is a complex disease state, management and treatment monitoring of PAI in pediatric patients must be in consultation with an endocrinologist or a healthcare provider with endocrine expertise.
 - IV. Differential diagnose of PAI requires confirmation with the Corticotropin simulation test, which is considered the gold standard due to its higher degree of specificity and sensitivity. A confirmed diagnosis of PAI is determined by low morning serum cortisol concentrations (≤ 140 nMol/L) and high adrenocorticotrophic hormone (ACTH) levels (≥ 66 pmol/L).
 - V. While glucocorticoid monotherapy is a typical initial treatment approach, many patients also require a mineralocorticoid as an add-on agent. The Journal of Endocrinology and Metabolism guideline recommends use of 100 μ g per day of fludrocortisone. Mineralocorticoids are essential in maintaining water and electrolyte homeostasis; however, use in PAI has not been studied systematically. The rationale is to dose fludrocortisone in the mornings to mimic aldosterone levels, which are generally high in the morning due to circadian rhythms.
 - VI. Patients with PAI are at high risk of developing Adrenal crisis, an acute etiology that develops due to inability of the adrenal gland to produce enough cortisol in response to an increased need. Clinical features of adrenal crisis consist of volume depletion and hypotension. In such cases, parenteral injections (50mg/m²) of hydrocortisone may be required.
 - VII. Hydrocortisone (Alkindi Sprinkle) received FDA approval for pediatric patients (<17 years of age) based on the ease of dosing and proposed accuracy of dosing as it is available in smaller doses (0.5 mg, 1 mg, 2 mg, and 5 mg). Hydrocortisone (Alkindi Sprinkle) was granted FDA-approval as a new dosage form of hydrocortisone and was limited to the indication of adrenocortical insufficiency. There are no independent prospective clinical trials to support efficacy and safety of hydrocortisone (Alkindi Sprinkle) for any other conditions. As such, until now, patients requiring a daily dose of hydrocortisone > 5 mg per day have been managed using hydrocortisone (Cortef) oral tablets (intact or crushed and mixed with liquid), or compounded formulations of hydrocortisone (oral solution or suspension). Notably, the compounded formulations of hydrocortisone have been successfully used in pediatric populations to fulfill the need for optimum daily doses less than 5 mg. These formulations provide accuracy of dosing as well as ease of administration. Although hydrocortisone (Alkindi Sprinkle) is a new formulation that provides administrative convenience, use of this formulation is cost-prohibitive. Given the long-standing efficacy, safety, accuracy of dosing, cost, and clinical experience, compounded formulations of hydrocortisone are considered standard and practical high-value treatment options in this space and should be preferred over hydrocortisone (Alkindi Sprinkle).

Investigational or Not Medically Necessary Uses

- I. There are no direct head-to-head clinical trials comparing efficacy and safety of glucocorticoid drugs used in in long term treatment of PAI in children. The Endocrine Societal Guidelines recommend children should be treated with hydrocortisone because of its optimal pharmacokinetic profile, and short half-life, furthermore overtreatment should be avoided.

Doses of ≥ 5 mg daily are considered not medically necessary for children aged less than 17 years of age due to risk of growth retardation. Therefore, close monitoring of glucocorticoid dosing is advised in children with increasing body surface area.

- II. Hydrocortisone (Alkindi Sprinkle) is not considered medically necessary in any other disease state other than adrenocortical insufficiency. Epidemiology in this setting largely involves pediatric population. Based on the scope of FDA-approval, hydrocortisone (Alkindi Sprinkle) is deemed medically necessary only for pediatric patients diagnosed with adrenocortical insufficiency, for whom, the total daily dose requirement may not be met using generic hydrocortisone tablets or compounded hydrocortisone formulations.
- III. Use of hydrocortisone has been widely recommended in many inflammatory conditions including chemotherapy induced nausea, prostate cancer, chronic lung disease and gout. However, it should be noted that typical daily dose requirement of hydrocortisone in the treatment of these conditions is higher than 5 mg per day. As such, use of hydrocortisone (Alkindi Sprinkle) in these settings over traditionally used hydrocortisone formulations (e.g. generic Cortef oral tablet) is not practical and FDA-approved, given the lack of the clinical superiority data for the former, as well as, higher cost of therapy.
- IV. Efficacy and Safety of hydrocortisones (Alkindi Sprinkle) for treatment of conditions other than adrenocortical insufficiency have not been studied and remain unknown.

References

1. Alkindi Sprinkle [Prescribing Information]. Eton Pharmaceutical: Deer Park, IL. June 2020.
2. Bronstein S, Allolio B, et al. Diagnosis and Treatment of Primary Adrenal insufficiency: An Endocrine Society Clinical Practice Guideline. A journal of Endocrinology and Metabolism.2016, February. Vol 10;364-389.
3. Reisch N, Willigie M, et al. Frequency and causes of adrenal crisis over lifetime in patients with 21-hydroxylase Deficiency. Eur j Endocrinol.2012;167:35-42
4. Stern JAC, Murthy S, et al: Who rapid evidence appraisal for COVID-19 Therapies (React) working group. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19. Meta-analysis. Jama. published online September 2,2020. Doi:10.1001/jama.2020.
5. Mentzelopoulos SD, Malachias S, et al: Vasopressin, steroids, and epinephrine and neurologically favorable survival after in hospital cardiac arrest: randomized clinical trial. Jama.2013;310(3):270-279
6. Annane D, Renault A, et al. Hydrocortisone plus Fludrocortisone for adults with septic shock. New England journal of Medicine.2018;378(9):809-818
7. Vandar- Heide Javing M, Kampus PJ et al. Short- and long-term effects of neonatal glucocorticoid therapy: is hydrocortisone an alternative to dexamethasone? Acta Paediatrica 2003; 92(7):827-835
8. Bonfig W, Pozza WF, et al. Hydrocortisone dosing during puberty in patients with Classical Congenital Hyperplasia: an evidence-based recommendation. J Clin Endocrinol Met.2009;94:3882-3884
9. Orange Book: approved drug products with therapeutic equivalence evaluations. U.S. Food & Drug Administration. Accessed November 2020. Available at: https://www.accessdata.fda.gov/scripts/cder/ob/search_product.cfm

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	12/2020

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP175

Description

Hydroxyprogesterone caproate is an injectable synthetic progestin.

Length of Authorization

- Initial:
 - i. Endogenous estrogen measurement, diagnosis: 2 months
 - ii. All other indications: 12 months
- Renewal:
 - i. Endogenous estrogen measurement, diagnosis: No renewal allowed
 - ii. All other indications: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
hydroxyprogesterone caproate*	1250 mg/5mL (250mg/mL)	Advanced adenocarcinoma of the uterus Amenorrhea Endometrial disorder Endogenous estrogen measurement, diagnosis	1 vial/28 days

**As of April 6, 2023, there is only one NDC of hydroxyprogesterone caproate FDA-approved for interstate commerce (67457-0886-05). All other NDCs have been discontinued by the FDA.*

Initial Evaluation

- I. **Hydroxyprogesterone caproate** may be considered medically necessary when the following criteria are met:
 - A. Member is age 18 years or older; **AND**
 - B. Member is NOT currently pregnant; **AND**
 - C. A diagnosis of one of the following:
 1. Advanced adenocarcinoma of the uterus (stage III or IV); **OR**
 2. Amenorrhea; **OR**
 3. Endometrial disorder (production of secretory endometrium and desquamation); **OR**
 4. Endogenous estrogen measurement test

- II. Hydroxyprogesterone caproate (Makena) is considered not medically necessary when criteria above are not met and/or when used for:
 - A. Reducing the risk of recurrent preterm birth

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 one of the following:
 - a. Advanced adenocarcinoma of the uterus (stage III or IV); **AND**
 - i. Member has exhibited disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread; **OR**
 - b. Amenorrhea; **OR**
 - c. Endometrial disorder (production of secretory endometrium and desquamation); **AND**
 - i. Member has exhibited improvement or stability of disease symptoms [e.g., normal menstrual bleeding]

Supporting Evidence

- I. Hydroxyprogesterone caproate was initially approved under the ANDA pathway as a therapeutic equivalent to the reference listed drug (RLD) Delalutin in 2015. The labeled indications approved are in non-pregnant adult women: for the treatment of advanced adenocarcinoma of the uterine corpus (Stage III or IV), in the management of amenorrhea (primary and secondary) and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as submucous fibroids or uterine cancer, as a test for endogenous estrogen production and for the production of secretory endometrium and desquamation.
- II. It should be noted that the RLD Delalutin has been discontinued and removed from the U.S. market in 2010. The U.S. Food and Drug Administration (FDA) noted in their approval letter for the generic equivalent that because the RLD Delalutin as not withdrawn from sale for reasons of safety or effectiveness, it allowed the agency to continue to approve applications that refer to Delalutin. The FDA concluded that adequate information had been presented to demonstrate hydroxyprogesterone caproate is safe and effective for use as recommended in the submitted labeling (noted above) and was subsequently approved.
- III. As of June 2023, there is only one hydroxyprogesterone caproate generic that is marketed in the U.S.; this product is manufactured by McGuff Pharmaceuticals for Mylan Institutional Inc.

Not Medically Necessary Uses

- I. Hydroxyprogesterone caproate has not demonstrated sufficient safety and efficacy for the conditions or settings listed below:
 - A. Reducing the risk of recurrent preterm birth

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These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

- i. As of April 6, 2023, the FDA announced their final decision to withdraw approval of Makena from the U.S. market, indicating that Makena and its generics (hydroxyprogesterone caproate) are no longer approved and cannot lawfully be distributed in interstate commerce. This decision was issued jointly by the FDA Commissioner and Chief Scientist after finding that there is an insufficient demonstration of effectiveness to balance any level of risk.
- ii. Hydroxyprogesterone caproate (Makena) was initially approved via the accelerated approval pathway based on the data from the NICHD-MFMU Network trial. The NICHD-MFMU Network trial was acquired by a pharmaceutical company (Adeza, Sunnyvale, CA) and submitted as part of a new drug application (NDA) to the Food and Drug Administration (FDA) in April 2006. In August 2006, an FDA Advisory Committee voted unanimously that an additional confirmatory clinical trial was required to further assess safety and efficacy.
- iii. Based on the FDA ruling, the NDA sponsor initiated the confirmatory clinical trial (PROLONG), enrolling 5% of the overall subjects prior to FDA approval. The study was designed to have the power to show a direct clinical benefit (i.e., a reduction in a prespecified neonatal morbidity and mortality index).
- iv. PROLONG is a Phase 3B, randomized double-blind parallel group study with a 2:1 ratio of active drug: vehicle, assigned randomly by a global telephone-based interactive registration system. Key inclusion criteria: at least 18 years of age, pregnant with a singleton gestation, documented history (chart notations from previous pregnancy and not just oral history) of singleton spontaneous preterm birth (PTB) between 200/7 and 366/7 weeks, after spontaneous PTB, or premature rupture of membranes. The primary safety outcome was fetal/early infant death defined as any of the following: spontaneous abortion/miscarriage (delivery from 160/7–196/7 weeks of gestation), stillbirth delivering after 200/7 weeks through term, or early infant death. The results of the PROLONG trial: fetal/early infant death rates were lower than expected and not different between treatment groups (17-OHPC 1.7% vs. placebo 1.9%; RR 0.87 [95% CI: 0.4–1.81]). No statistically significant difference in the frequency of stillbirth (17-OHPC 1.1% vs placebo 0.5%; RR 2.07 [95% CI 0.59–7.29])
- v. On October 5, 2020, The Center for Drug Evaluation and Research (CDER) proposed withdrawing accelerated approval of Makena (hydroxyprogesterone caproate) on the grounds that the confirmatory study failed to verify clinical benefit of the drug and the evidence does not establish that the drug is effective under its conditions of use. A hearing took place in October 2022 where the advisory committee discussed and voted on whether the findings from PROLONG verify the clinical benefit of Makena and if the available evidence demonstrates that Makena is effective for its approved indication. The advisory committee voted unanimously that the PROLONG trial does not verify the clinical benefit of Makena, and 13 advisory committee members voted that the available evidence does not demonstrate that Makena is effective for its approved indication, with one member voting ‘yes’ and one member ‘abstained’. Finally, 14 advisory committee members voted that Makena should not remain on the market while

an appropriate confirmatory study is designed and conducted, while one member voted 'yes'. Most advisory committee members agreed during discussion that there was not sufficient evidence that Makena is effective in any population.

- vi. Given the lack of efficacy for reducing the risk of preterm birth and the subsequent decision by the FDA to withdraw the indication, treatment with hydroxyprogesterone caproate for risk reduction in recurrent preterm birth is not medically necessary.

References

1. Hydroxyprogesterone caproate [Prescribing Information]. Morgantown, WV: Mylan Institutional LLC. November 2021.
2. Food and Drug Administration, HHS. Final Decision on Withdrawal of Makena (hydroxyprogesterone caproate) and Eight Abbreviated New Drug Applications Following Public Hearing; Availability of Final Decision. Federal Register. 2023;88(93), 30986-87. Available at: <https://www.regulations.gov/document/FDA-2020-N-2029-0386>.
3. Food and Drug Administration. Memorandum; Termination of Separation of Functions and Process for Issuing a Final Decision; Makena. Updated April 5, 2023. Available at: <https://www.regulations.gov/document/FDA-2020-N-2029-0384>.
4. Food and Drug Administration. Final Decision on the Proposal to Withdraw Approval of Makena. Updated April 5, 2023. Available at: <https://www.regulations.gov/document/FDA-2020-N-2029-0385>.
5. Food and Drug Administration. FDA Commissioner and Chief Scientist Announce Decision to Withdraw Approval of Makena. Fda.gov. April 6, 2023. Accessed May 15, 2023. <https://www.fda.gov/news-events/press-announcements/fda-commissioner-and-chief-scientist-announce-decision-withdraw-approval-makena>.
6. Blackwell SC, Gyamfi-Bannerman C, Biggio JR Jr, et al. PROLONG Clinical Study Protocol: Hydroxyprogesterone Caproate to Reduce Recurrent Preterm Birth. Am J Perinatol. 2018;35(12):1228–1234. doi:10.1055/s-0038-1642062
7. Blackwell SC, Gyamfi-Bannerman C, Biggio JR Jr, et al. 17-OHPC to Prevent Recurrent Preterm Birth in Singleton Gestations (PROLONG Study): A Multicenter, International, Randomized Double-Blind Trial [published online ahead of print, 2019 Oct 25]. Am J Perinatol. 2019;10.1055/s-0039-3400227. doi:10.1055/s-0039-3400227
8. Meis PJ, Klebanoff M, Thom E, et al; National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. N Engl J Med 2003;348 (24):2379–2385

Policy Implementation/Update:

Action and Summary of Changes	Date
Criteria for medical necessity of hydroxyprogesterone caproate (Makena) removed; use of hydroxyprogesterone caproate (Makena) for reducing risk of recurrent preterm birth moved to not medically necessary section; criteria added for medical necessity of hydroxyprogesterone caproate (therapeutic equivalent of Delalutin); supporting evidence updated	06/2023
Policy created	02/2020

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP269

Description

ibrexafungerp (Brexafemme) is an orally administered triterpenoid antifungal.

Length of Authorization

- Initial:
 - i. Acute vulvovaginal candidiasis (VVC): one month
 - ii. Recurrent vulvovaginal candidiasis (RVVC): 6 months
- Renewal: Cannot be renewed

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
ibrexafungerp (Brexafemme)	Treatment of vulvovaginal candidiasis (VVC)	150mg tablet	4 tablets/1 day
	Reduction in the incidence of recurrent vulvovaginal candidiasis (RVVC)		

Initial Evaluation

- I. **Ibrexafungerp (Brexafemme)** may be considered medically necessary when the following criteria are met:
 - A. Member is 12 years of age or older; **AND**
 - B. Member has experienced menarche; **AND**
 - C. A diagnosis of one of the following:
 1. **Acute vulvovaginal candidiasis (VVC); AND**
 - i. Treatment with fluconazole 150mg (Diflucan) has been ineffective, contraindicated, or not tolerated; **OR**
 2. **Recurrent vulvovaginal candidiasis (RVVC); AND**
 - i. Member has a history of three or more acute vulvovaginal candidiasis (VVC) episodes within the last 12 months; **AND**
 - ii. Member is currently experiencing signs and symptoms consistent with an acute episode of VVC (e.g., vulvovaginal pain, pruritis or irritation, abnormal vaginal discharge, etc.); **AND**
 - iii. Diagnosis of acute VVC has been confirmed by positive KOH or culture; **AND**
 - iv. Member has been treated with weekly oral fluconazole for a period of 6 months; **OR**
 - a. Treatment with fluconazole is not tolerated or contraindicated; **OR**

- b. Antifungal susceptibility testing has been conducted and confirms fluconazole resistance; **OR**
 - c. Member has experienced a recurrence during or following maintenance therapy with fluconazole
- II. Ibrexafungerp (Brexafemme) is considered investigational when used for all other conditions, including but not limited to:
 - A. Allergic bronchopulmonary aspergillosis
 - B. Blastomycosis
 - C. Coccidioidomycosis
 - D. Histoplasmosis
 - E. Invasive candidiasis
 - F. Invasive and/or chronic pulmonary aspergillosis
 - G. Mucocutaneous candidiasis

Renewal Evaluation

- I. Please see initial evaluation

Supporting Evidence

- I. Ibrexafungerp (Brexafemme) was initially approved by the FDA in 2021 for the treatment of acute vulvovaginal candidiasis (VVC) in adult and post-menarche pediatric females. In 2022, the FDA granted approval for a second indication, reduction in the incidence of recurrent vulvovaginal candidiasis (RVVC).
- II. **Acute Vulvovaginal Candidiasis**
 - In the setting of acute VVC, ibrexafungerp (Brexafemme) was studied in two identically designed randomized, double-blind, placebo-controlled, Phase 3 trials in 558 total post-menarche females aged 12 years and older (VANISH-303 and VANISH-306). The primary efficacy outcome was clinical cure (defined as complete resolution of signs and symptoms) at day 10 test-of-cure (TOC) visit. The key secondary outcomes included mycological eradication (negative culture for growth of yeast [candida species]) at TOC and clinical cure at follow-up visit (day 25). Ibrexafungerp (Brexafemme) was statistically significant compared to placebo for all primary and key secondary endpoints in both the VANISH-303 and VANISH-306 trials.
 - Ibrexafungerp (Brexafemme) was also studied against fluconazole in a Phase 2b, multicenter, randomized, double-blind, double-dummy, active-controlled, dose-finding study (DOVE) in 186 patients with moderate-to-severe acute VVC. The primary endpoint was percentage of patients with clinical cure at the TOC (day 10), which was 53% for ibrexafungerp (Brexafemme) and 58% for fluconazole. This study was not statistically powered; thus, the clinical significance of these results cannot be determined.

III. **Recurrent Vulvovaginal Candidiasis**

- In the setting of RVVC, ibrexafungerp (Brexafemme) was studied in one randomized, double-blind, placebo-controlled trial (CANDLE) of 260 post-menarche females aged 12 years and older who had a diagnosis of RVVC, defined as at least three prior episodes of acute VVC in the past 12 months. The trial consisted of an acute phase and a maintenance phase. All patients received fluconazole 150mg on days 1, 4, and 7 during the acute phase to treat their current infection. Patients who responded to fluconazole therapy with significant resolution of their vulvovaginal signs and symptoms, defined as total composite score of ≤ 2 on the VSS Scale) then entered the maintenance phase. Patients in the maintenance phase were randomized to receive ibrexafungerp (Brexafemme) or placebo once monthly for 6 months.
 - The primary endpoint was percentage of patients with clinical success (defined as no mycologically proven, presumed, or suspected recurrence of VVC) up to the test-of-cure (TOC) visit at week 24 post-dose. The secondary endpoint was percentage of patients with no mycologically proven recurrence (defined as an episode of VVC with total composite VSS Score of ≥ 3 and a culture positive for *Candida* spp. That required antifungal treatment), also at TOC (24 weeks). For the primary endpoint, 65.4% of patients in the ibrexafungerp (Brexafemme) group met the primary endpoint compared to 53.1% of patients in the placebo group ($p=0.02$); this was sustained over the three-month follow-up period ($p=0.034$). For the secondary endpoint, 70.8% of patients in the ibrexafungerp (Brexafemme) group met the secondary endpoint compared to 58.5% of patients in the placebo group ($p=0.019$), which was also sustained over the follow-up period ($p=0.029$).
- IV. Patients enrolled in the trial were aged 12 years and older who had already experienced menarche (i.e., first menstrual cycle). The safety and/or efficacy of ibrexafungerp (Brexafemme) in pediatric patients who are either under the age of 12 years or have not experienced menarche has not been evaluated.
- V. The safety profile for ibrexafungerp (Brexafemme) was consistent between the acute VVC and RVVC trials. The most commonly reported side effects include diarrhea (~15%), nausea (~11%), abdominal pain (~11%), headache (~17%), and dizziness (~2%). Although ibrexafungerp (Brexafemme) carries a contraindication for use during pregnancy due to risk of embryo-fetal toxicity, women of childbearing age were included in the clinical trial and were advised to not become pregnant during the trial duration. FDA label recommends verifying pregnancy status prior to initiating therapy with ibrexafungerp (Brexafemme), and prior to each dose when using for RVVC.
- VI. Clinical guidelines, including those published by the Centers for Disease Control and Prevention (CDC) and Infectious Disease Society of America (IDSA), indicate that diagnosis of VVC can typically be made via the presentation of infection signs/symptoms: pruritis, irritation, vaginal soreness, external dysuria, and dyspareunia accompanied by signs of vulvar edema, erythema, excoriation, fissures and white, thick, curd-like vaginal discharge. For complicated VVC and RVVC, diagnosis should be confirmed with a wet-mount preparation with use of saline and 10% potassium hydroxide (KOH). If KOH is negative, a culture for *Candida* should be obtained.
- VII. For the treatment of acute VVC, IDSA and CDC guidelines carry a strong recommendation for topical (intravaginal) antifungals or oral fluconazole 150mg for acute, uncomplicated VVC. The

same medications can be used for complicated and/or recurrent VVC, but at extended treatment durations of 10 – 14 days. Topical antifungals, such as miconazole and clotrimazole, are available in multiple over the counter (OTC) formulations, while oral fluconazole remains prescription only.

- VIII. RVVC is usually defined as having at least three episodes of acute VVC within one year and are typically caused by azole-susceptible *C. albicans*. Clinical guidelines recommend beginning treatment with induction therapy with a 10-to-14-day course of a topical azole or oral fluconazole, followed by maintenance therapy with fluconazole 150mg once weekly for six months. If oral fluconazole is not feasible, topical clotrimazole (200mg cream twice weekly or 500mg vaginal suppository once weekly) or other intermittent oral or topical antifungal treatment is recommended. After cessation of maintenance therapy, IDSA approximates a 40-50% recurrence rate. Ibrexafungerp (Brexafemme) may be considered medically necessary if oral fluconazole has been not tolerated, is contraindicated, fluconazole resistance is confirmed, or if members experience recurrence of acute VVC symptoms anytime during or after maintenance therapy with fluconazole.
- IX. According to results of the CANDLE trial, nearly 70% of participants who completed the maintenance regimen with ibrexafungerp (Brexafemme) did not experience a recurrent episode for up to 36 weeks (approximately nine months). However, rates of recurrence beyond nine months or safety and efficacy of retreatment with ibrexafungerp (Brexafemme) has not been established. Due to lack of adequate safety and efficacy data to establish an appropriate timeline for retreatment, renewal requests will be evaluated against initial policy criteria.

Investigational or Not Medically Necessary Uses

- I. Ibrexafungerp (Brexafemme) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Allergic bronchopulmonary aspergillosis
 - B. Blastomycosis
 - C. Coccidioidomycosis
 - D. Histoplasmosis
 - E. Invasive candidiasis
 - F. Invasive and/or chronic pulmonary aspergillosis
 - G. Mucocutaneous candidiasis

References

1. Centers for Disease Control and Prevention (CDC). 2015 Sexually Transmitted Diseases Treatment Guideline: Vulvovaginal candidiasis. Accessed July 19, 2021.
2. Pappas PG, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. *Clinical Infectious Diseases*. 2016;62(4):e1-50.
3. Azie N, et al. Efficacy and Safety of oral ibrexafungerp (SCY-078) vs. Placebo in Subjects with Acute Vulvovaginal Candidiasis (VANISH 303). Scynexis, Inc. 2020. [presented at ACOG Annual Clinical and Scientific Meeting, May 2021].
4. Sobel R, et al. Efficacy and Safety of oral ibrexafungerp (SCY-078) vs. Placebo in Subjects with Acute Vulvovaginal Candidiasis (VANISH 306). Scynexis, Inc. 2020. [presented at ACOG Annual Clinical and Scientific Meeting, May 2021].

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5. New Drug Review: ibrexafungerp (Brexafemme). IPD Analytics. June 2021.
6. Cadet R, et al. A Phase 2b, dose-finding study evaluating oral ibrexafungerp vs fluconazole in vulvovaginal candidiasis (DOVE). *Obstet Gynecol.* 2019;133 (suppl):113S–114S.
7. Centers for Disease Control and Prevention (CDC). 2015 Sexually Transmitted Diseases Treatment Guideline: Vulvovaginal candidiasis. Accessed July 19, 2021.
8. Pappas PG, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. *Clinical Infectious Diseases.* 2016;62(4):e1-50.
9. Brexafemme [Prescribing Information]. Scynexis, Inc.: Jersey City, NJ. November 2022.
10. Scynexis, Inc. Ibrexafungerp: a novel oral triterpenoid antifungal for the treatment of patients with vulvovaginal candidiasis (VVC). AMCP Dossier. June 30, 2021.

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
oteseconazole (Vivjoa™)	Recurrent vulvovaginal candidiasis (RVVC)

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	03/2023

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP037

Split Fill Management*

Description

Ibrutinib (Imbruvica) is an orally administered Bruton's tyrosine kinase (BTK) inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
ibrutinib (Imbruvica)	Chronic Graft versus Host Disease (refractory); Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma; Waldenström Macroglobulinemia	420 mg tablets	28 tablets/28 days
	Chronic Graft versus Host Disease (refractory)	70mg/mL suspension	216mL/35 days**
	Dose modification	280 mg tablets	56 tablets/28 days
	Dose modification	140 mg tablets	112 tablets/28 days
	Dose modification	140 mg capsules	120 capsules/30 days
	Dose modification	70 mg capsules	30 capsules/30 days

****Body surface area (BSA) dosing under 12 years of age:** 240 mg/m² once daily; maximum dose: 420 mg/dose. Due to the unbreakable packaging, 216mL/35 days is the maximum dosing. Those 12 and older should use 420mg tablets.

Initial Evaluation

- I. **Ibrutinib (Imbruvica)** may be considered medically necessary when the following criteria below are met:
 - A. Treatment is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
 - B. If the request is for the 140 mg tablets or 280 mg tablets, there is documentation that the member has tried and failed or has a contraindication to the 140 mg capsules; **OR**
 1. If the request is for the 70mg/mL suspension, the patient is under 12 years of age; **AND**
 - C. Member has not experienced disease progression while on a BTK inhibitor [e.g., zanubrutinib (Brukinsa), acalabrutinib (Calquence)]; **AND**
 - D. A diagnosis of one of the following:
 1. **Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL); AND**
 - i. Member is 18 years of age or older; **AND**
 - ii. The member does not have a 17p deletion or TP53 mutation confirmed by testing; **AND**

- a. Ibrutinib (Imbruvica) will be used as monotherapy; **OR**
 - i. The request is for use in combination with bendamustine and rituximab in the relapsed/refractory setting; **OR**
 - iii. The member has a 17p deletion or TP53 mutation confirmed by testing; **AND**
 - a. Ibrutinib (Imbruvica) will be used as monotherapy; **OR**
 - 2. **Waldenström Macroglobulinemia (WM); AND**
 - i. Member is 18 years of age or older; **AND**
 - ii. Ibrutinib (Imbruvica) will be used as monotherapy; **OR**
 - iii. Ibrutinib (Imbruvica) will be used with rituximab; **OR**
 - 3. **Chronic Graft versus Host Disease (cGVHD); AND**
 - i. Member is one year of age or older; **AND**
 - ii. Member has failed one or more lines of systemic therapy (e.g., corticosteroids, mycophenolate mofetil, calcineurin inhibitors, sirolimus)
- II. Ibrutinib (Imbruvica) is considered not medically necessary when criteria above are not met and/or when used for:
 - A. Chronic lymphocytic leukemia/small lymphocytic lymphoma in combination with rituximab only
 - B. Mantle cell lymphoma (new to therapy)
 - C. Marginal zone lymphoma (new to therapy)
- III. Ibrutinib (Imbruvica) is considered investigational when used for all other conditions, including but not limited to:
 - A. Chronic lymphocytic leukemia/small lymphocytic lymphoma in the first line setting in combination with obinutuzumab
 - B. Relapsed/refractory Hodgkin lymphoma
 - C. Diffuse large B cell lymphoma
 - D. Relapsed/refractory multiple myeloma
 - E. Hairy cell leukemia
 - F. Primary CNS lymphoma
 - G. Esophagogastric carcinoma
 - H. Glioblastoma
 - I. Non-small-cell lung carcinoma
 - J. T-cell lymphoma

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. If the request is for the 140 mg tablets or 280 mg tablets, the member has tried and failed or has a contraindication to the 140 mg capsules; **OR**

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- If the request is for the 70mg/mL suspension, the member under the age of 12 years; **AND**
- IV. The member has exhibited improvement of their condition defined as:
- **For GVHD:** The member has exhibited improvement or stability of symptoms [e.g., manifestations of disease to the skin, oral cavity, musculoskeletal system]; **OR**
 - **For oncology indications:** The member has not experienced disease progression while on ibrutinib (Imbruvica); **OR**
- V. Compelling clinical evidence of benefit is provided if therapy is to be continued after disease progression.

Supporting Evidence

- I. NCCN guidelines note that acquired resistance to ibrutinib (Imbruvica) is mediated by BTK mutations, which have also been described in patients receiving other BTK inhibitors (e.g., acalabrutinib [Calquence], zanubrutinib [Brukinsa]).
- II. The safety and efficacy of ibrutinib (Imbruvica) in patients with CLL/SLL were demonstrated in one uncontrolled trial and four randomized, controlled trials.
 - The RESONATE study, was a randomized, multicenter, open-label, phase 3 study of ibrutinib (Imbruvica) versus ofatumumab in patients with relapsed or refractory CLL/SLL. With an overall follow-up of 63 months, the median PFS was 44.1 months [95% CI (38.5, 56.9)] in the ibrutinib (Imbruvica) arm and 8.1 months [95% CI (7.8, 8.3)] in the ofatumumab arm, respectively. RESONATE included 127 patients with del17p CLL/SLL, PFS at 63 months was 40.6 months [95% CI (25.4, 44.6)] in the ibrutinib (Imbruvica) arm and 6.2 months [95% CI (4.6, 8.1)] in the ofatumumab arm.
 - The RESONATE-2 study, a randomized, multicenter, open-label, phase 3 study versus chlorambucil in patients 65 years or older with treatment-naïve CLL/SLL (n=269) reported an overall survival analysis in the intention to treat patient population which resulted in a statistically significant HR of 0.44 [95% CI (0.21, 0.92)] and 2-year survival rate estimates of 94.7% [95% CI (89.1, 97.4)] and 84.3% [95% CI (76.7, 89.6)] in the ibrutinib (Imbruvica) and chlorambucil arms, respectively.
 - The HELIOS study was a randomized, double-blind, placebo-controlled, Phase 3 trial of ibrutinib (Imbruvica) in combination with bendamustine and rituximab in 578 patients with relapsed or refractory CLL/SLL. Patients with del17p were excluded. The primary efficacy endpoint was PFS. Ibrutinib (Imbruvica) in combination with bendamustine and rituximab had a median PFS that was not evaluable compared to 13.3 months for ibrutinib (Imbruvica) in combination with placebo. The HR was 0.20 (95% CI 0.15, 0.28) for PFS.
 - NCCN CLL/SLL guidelines recommend ibrutinib (Imbruvica) monotherapy as a Category 1 recommendation in the relapsed/refractory setting in patients with or without 17p deletion/TP53 mutation. In the first-line setting monotherapy also carries a Category 1 recommendation in patients without 17p deletion/TP53 mutation, with a 2A recommendation in those with the deletion/mutation. NCCN guidelines do not list combination ibrutinib (Imbruvica) with rituximab, ibrutinib

- (Imbruvica) with rituximab and bendamustine, or ibrutinib (Imbruvica) with obinutuzumab in members with 17p deletion/TP53 mutation as a treatment option.
- III. The safety and efficacy of ibrutinib (Imbruvica) in patients with WM were demonstrated in two single-arm trials and one randomized, controlled trial. Study 1118, an open-label, multi-center, single-arm trial of 63 previously treated patients reported a response rate of 61.9%. The INNOVATE monotherapy arm included 31 patients with previously treated WM who failed prior rituximab-containing therapy and received single-agent ibrutinib (Imbruvica). The response rate observed in the INNOVATE monotherapy arm was 71%, with a median follow-up time on study of 34 months. The INNOVATE study, a randomized, double-blind, placebo-controlled, phase 3 study of ibrutinib (Imbruvica) or placebo in combination with rituximab in subjects with treatment naïve or previously treated WM. The primary endpoint of progression-free survival (PFS) was 82% with ibrutinib–rituximab versus 28% with placebo–rituximab (hazard ratio for progression or death, 0.20; P<0.001).
 - IV. The safety and efficacy of ibrutinib (Imbruvica) in cGVHD was shown in two clinical trials. One being the confirmatory FDA approval trial for adults and the second was a safety trial for an age expansion in pediatrics.
 - Ibrutinib (Imbruvica) was studied in an open-label, multi-center, single-arm trial of 42 adult (18 and over) patients with cGVHD after failure of first line corticosteroid therapy and requiring additional therapy; patients received 420mg of ibrutinib daily. Therapy with ibrutinib (Imbruvica) resulted in an ORR of 67%. Corticosteroids are the mainstay of initial systemic treatment for patients with cGVHD. Alternatives to, or add-on therapy to, corticosteroids include, but are not limited to, mycophenolate mofetil, calcineurin inhibitors (e.g., cyclosporine, tacrolimus), and sirolimus.
 - In 2022, ibrutinib (Imbruvica) was studied in an open-label, multi-center, single arm trial in pediatric patients aged between 1 year and 22 years with moderate to severe cGVHD. The trial enrolled 47 patients who required additional therapy after failure of one or more prior lines of systemic therapy (e.g. cyclosporine, tacrolimus). Patients 12 and older were treated with 420mg once daily and those 1 year to under 12 were treated with 240mg/m² once daily, with a maximum dose of 420mg. The ORR through week 25 was 60%. Additionally, there were no new safety signals compared to the adult confirmatory trial.
 - V. For several indications and trials, the rate of discontinuation/dose reduction/dose interruption was greater than 20% of the population studied. The high rate of discontinuation meets the requirements for split-fill criteria.

Investigational or Not Medically Necessary Uses

- I. Ibrutinib (Imbruvica) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below.

Not Medically Necessary Uses

- A. Chronic lymphocytic leukemia/small lymphocytic leukemia, in combination with rituximab
 - i. In the E1912 trial, ibrutinib (Imbruvica) in combination with rituximab, showed significant improvements in PFS compared to fludarabine, cyclophosphamide, and rituximab chemoimmunotherapy. The primary endpoint was PFS, and the HR for

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disease progression was 0.34 (95% CI 0.22, 0.52). The results of the Phase 3 Alliance North American Intergroup Study (A041202) comparing ibrutinib (Imbruvica) monotherapy to ibrutinib (Imbruvica) + rituximab found the estimate 2-year PFS rates were 87% and 88% ($p=0.49$), respectively. NCCN guidelines note that the addition of rituximab to ibrutinib has not yet demonstrated improvement in clinical outcomes compared to ibrutinib monotherapy in a randomized clinical trial. The consensus was that the longer PFS in combination trials was more the result of continuous and indefinite treatment with ibrutinib, rather than due to the contribution of rituximab. There is a consideration that improved outcomes with the addition of anti-CD20 monoclonal antibodies may more likely be seen with fixed-duration treatment with these regimens.

B. Mantle cell lymphoma (MCL)

- i. Ibrutinib (Imbruvica) was previously FDA-approved under the accelerated approval pathway for the treatment of adult patients with MCL who have received at least one prior therapy. This indication approval was based on overall response rate and continued approval was contingent upon verification and description of clinical benefit in confirmatory trials. The confirmatory phase 3 trial (SHINE) met the primary endpoint of progression-free survival but failed to show significant overall survival benefit in patients treated with combination of ibrutinib (Imbruvica), bendamustine, and rituximab compared to patients treated with combination of placebo, bendamustine, and rituximab. Overall survival at 7 years was 55% in the ibrutinib (Imbruvica) group and 56.8% in the placebo group. Moreover, the addition of ibrutinib (Imbruvica) to chemotherapy was associated with increased adverse reactions compared to placebo-controlled group. After discussion of the results with the FDA, AbbVie voluntarily withdrew the U.S. accelerated approval for patients with MCL as the confirmatory study was insufficient to support conversion to full approval. Requests for initiation of ibrutinib (Imbruvica) for the treatment of MCL are considered not medically necessary due to a failed confirmatory Phase 3 trial and lack of continued FDA approval. Patients currently receiving ibrutinib (Imbruvica) and experiencing benefit from therapy are eligible for renewal and continued use for the treatment of MCL.
- ii. Ibrutinib (Imbruvica) was also studied against temsirolimus in one randomized, open-label, multi-center, Phase 3 trial in patients with relapsed or refractory MCL. Data is available for three years of follow up. Median progression free survival (PFS) was significantly longer for ibrutinib (Imbruvica) than temsirolimus (15.6 vs 6.2 months; HR 0.45 [95% CI 0.35–0.60]; $P < 0.0001$). Overall survival (OS) data was not statistically significant but favored ibrutinib (Imbruvica) numerically (30.3 vs 23.5 months, respectively; HR 0.74 [95% CI 0.54–1.02]; $P = 0.0621$).

Ongoing studies of ibrutinib (Imbruvica) for the treatment of MCL:

- iii. Mantle cell lymphoma, frontline
 1. Ibrutinib (Imbruvica) is being investigated as a first-line treatment in patients up to 65 years of age in the European TRINANGLE trial (NCT02858258). The study evaluates the addition of ibrutinib (Imbruvica)

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in the induction phase and as maintenance, as well as if autologous stem cell transplant may be omitted. Three-year results have been reported at the 2022 American Society of Hematology Annual meeting, however, longer follow up is needed to confirm benefit.

2. Ibrutinib (Imbruvica) is being investigated as a first line treatment in a Phase 2/3 trial (ENRICH) in patients over 60 years of age with MCL. The trial is comparing ibrutinib combined with rituximab, followed by rituximab maintenance against rituximab combined with chemotherapy, followed by rituximab maintenance. ENRICH is fully enrolled but there are no data available yet.
- iv. Mantle cell lymphoma, combination therapy.
1. Ibrutinib (Imbruvica) was studied in an open-label, single-arm, Phase 2 trial in combination with rituximab in patients with relapsed or refractory MCL and in patients over 65 years of age with newly-diagnosed, untreated MCL. At a median follow-up of 16.5 months, 44 (88%, 95% CI 75.7-95.5) patients achieved an objective response. Additional studies are needed to further evaluate and support this combination use.
 2. Combination of ibrutinib (Imbruvica), lenalidomide, and rituximab was studied in one open-label, single-arm, Phase 2 trial in patients with relapsed or refractory MCL who had previously been treated with at least one rituximab-containing regimen. The primary endpoint, ORR at 17.8 months was achieved in 38 (76%, 95% CI 63-86) patients. Additional studies are needed to further evaluate and support this combination use.
 3. A Phase 2 study of ibrutinib (Imbruvica) plus venetoclax in relapsed or refractory MCL patients (n=23), found the primary endpoint of complete response rate at week 16 was 42%, which was higher than the historical control of 9% at this time point with ibrutinib (Imbruvica) monotherapy (P<0.001). Additional studies are needed to further evaluate and support this combination use.

C. Marginal zone lymphoma (MZL)

- i. In the setting of MZL, ibrutinib (Imbruvica) was FDA-approved under accelerated approval pathway based on an open-label, multi-center, single-arm trial (PCYC-1121) of 63 adult patients who received at least one prior therapy, including one anti-CD20-directed regimen. The confirmatory phase 3 study (SELENE; NCT01974440) in patients with relapsed/refractory follicular lymphoma or MZL did not meet its primary endpoint of progression-free survival in patients with R/R FL or MZL. The SELENE study results will be presented at a future scientific forum. After discussion of the results with the FDA, AbbVie voluntarily withdrew the U.S. accelerated approval for patients with MZL as the confirmatory study was insufficient to support conversion to full approval. Requests for initiation of ibrutinib (Imbruvica) for the treatment of MZL are considered not medically necessary due to a failed confirmatory Phase 3 trial and lack of continued FDA approval. Patients currently receiving ibrutinib (Imbruvica) and experiencing

benefit from therapy are eligible for renewal and continued use for the treatment of MZL.

Ongoing studies of ibrutinib (Imbruvica) for the treatment of MZL:

- i. Marginal zone lymphoma, frontline
 - 1. Ibrutinib (Imbruvica) has not been sufficiently studied in treatment naïve patients with MZL. A Phase 3, double-blind, placebo-controlled study evaluating ibrutinib (Imbruvica) in combination with rituximab in treatment naïve patients is currently underway with estimated completion date of June 30, 2024 (NCT04212013). Additionally, a Phase 2, single-arm, open-label trial (MALIBU) evaluating ibrutinib (Imbruvica) in combination with rituximab is also underway with expected completion date of June 15, 2024 (NCT03697512).

Investigational

- A. Chronic lymphocytic leukemia/small lymphocytic lymphoma in the first line setting in combination with obinutuzumab
 - ii. The iLLUMINATE study was a randomized, open-label, active-controlled, multicenter, Phase 3 trial of ibrutinib (Imbruvica) in combination with obinutuzumab studied against chlorambucil in combination with obinutuzumab in 229 patients with treatment naïve CLL/SLL. Patients were either aged 65 years or older or younger than 65 years with coexisting conditions. The primary efficacy outcome was PFS. Ibrutinib (Imbruvica) in combination with obinutuzumab, had a median PFS that was not evaluable, compared to 19 months for chlorambucil in combination with obinutuzumab. The HR was 0.23 (95% CI 0.13, 0.37) for PFS. There have been no direct comparisons between ibrutinib (Imbruvica) monotherapy and ibrutinib (Imbruvica) in combination with obinutuzumab, therefore, it is not known if combination of the two agents will provide superior efficacy outcomes than ibrutinib (Imbruvica) monotherapy. Additionally, NCCN guidelines state that longer PFS may be the result of continuous and indefinite treatment with ibrutinib, rather than due to contribution of an anti-CD20 mAb during the first six months of treatment. There is a consideration that improved outcomes with the addition of anti-CD20 monoclonal antibodies may more likely be seen with fixed-duration treatment with these regimens. NCCN guidelines recommend ibrutinib (Imbruvica) + obinutuzumab (for frail patients with significant comorbidities and patients aged ≥65 years and younger patients with significant comorbidities) and ibrutinib + rituximab (for patients <65 years without significant comorbidities) as a 2B (other recommended regimens) recommendation.
- B. Relapsed/refractory Hodgkin lymphoma
 - iii. Subject of current ongoing trials.
- C. Diffuse large B cell lymphoma
 - iv. Ibrutinib (Imbruvica) was studied in a phase 1/2 clinical trial that involved 80 subjects with relapsed or refractory DLBCL, ibrutinib (Imbruvica) produced complete or partial responses in 37% (14/38) of those with activated B cell–like

- (ABC) DLBCL, but in only 5% (1/20) of subjects with germinal center B cell–like (GCB) DLBCL (P = 0.0106). Additional studies are needed and are currently underway, as ibrutinib (Imbruvica) is the subject of several ongoing phase 2 trials in the relapsed/refractory setting.
- v. The addition of ibrutinib (Imbruvica) to standard R-CHOP chemotherapy regimen in the DLBCL first-line setting failed to meet its primary endpoint of improving event-free survival (EFS) when compared to R-CHOP alone in the phase III PHOENIX (NCT01855750) study.
- D. Relapsed/refractory multiple myeloma
- vi. Ibrutinib (Imbruvica) was studied in a phase 2 study that examined various doses of ibrutinib (Imbruvica) ± low-dose dexamethasone in patients who received ≥2 prior lines of therapy, including an immunomodulatory agent. The primary objective of clinical benefit rate (CBR; ≥minimal response) was the highest (CBR 28%) in Cohort 4 which consisted of ibrutinib (Imbruvica) + dexamethasone (n=43). Further evaluation is needed to support use of ibrutinib (Imbruvica) in this setting.
- E. Hairy cell leukemia
- vii. Ibrutinib (Imbruvica) was subject of a single arm phase two study (n=28) in patients with hairy cell leukemia stage 1. The primary overall objective response rate, was seen in 46%, with objective responses more commonly seen in those patients with classical hairy cell leukemia (c-HCL). Additional studies are needed to further evaluate and support this use.
- F. Primary CNS lymphoma
- viii. Ibrutinib (Imbruvica) was subject of a phase 1 trial in patients (n=13) with relapsed or refractory CNS lymphoma. Additional studies are needed to further evaluate and support this use.
- G. Esophagogastric carcinoma
- ix. Ibrutinib (Imbruvica) is subject of ongoing trials in this setting.
- H. Glioblastoma
- x. Ibrutinib (Imbruvica) is subject of ongoing trials in this setting.
- I. Non-small-cell lung carcinoma
- xi. Ibrutinib (Imbruvica) is subject of ongoing trials in this setting.
- J. T-cell lymphoma
- xii. Ibrutinib (Imbruvica) is subject of ongoing trials in this setting.

** 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.*

Related Policies

Policy Name	Disease state
ruxolitinib (Jakafi®)	Chronic Graft versus Host Disease
belumosudil (Rezurock™)	
acalabrutinib (Calquence®)	Mantle cell lymphoma; CLL; SLL
lenalidomide (Revlimid®); pomalidomide (Pomalyst®); thalidomide (Thalomid®)	Mantle cell lymphoma; marginal zone lymphoma
zanubrutinib (Brukinsa™)	Mantle cell lymphoma; Waldenstrom's macroglobulinemia; marginal zone lymphoma' CLL, SLL

References

1. Imbruvica [package insert]. Horsham, PA: Janssen Biotech, Inc.; April, 2020; revised August 2022.
2. National Comprehensive Cancer Network. NCCN Clinical Practice Guideline in Oncology. Chronic lymphocytic leukemia/Small lymphocytic lymphoma Version 4.2020. January 2, 2020.
3. Wang ML, Rule S, Martin P, et al. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. N Engl J Med. 2013;369(6):507-16.
4. Moreno C, Greil R, Demirkan F, et al. Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol. 2019;20(1):43-56.
5. Dimopoulos MA, Tedeschi A, Trotman J, et al. Phase 3 Trial of Ibrutinib plus Rituximab in Waldenström's Macroglobulinemia. N Engl J Med. 2018;378(25):2399-2410.
6. National Comprehensive Cancer Network. NCCN Clinical Practice Guideline in Oncology. B-cell lymphomas. Version 5.2022. July 12, 2022.
7. Wilson WH, Young RM, Schmitz R, et al. Targeting B cell receptor signaling with ibrutinib in diffuse large B cell lymphoma. Nat Med. 2015;21(8):922-6.
8. AbbVie Provides Update on Phase 3 Study of Ibrutinib (IMBRUVICA®) in Blood Cancer Diffuse Large B-Cell Lymphoma (DLBCL) and Ongoing Ibrutinib Clinical Program. Abbvie Press Release. July 2018. Available at: <https://news.abbvie.com/news/abbvie-provides-update-on-phase-3-study-ibrutinib-imbruvica-in-blood-cancer-diffuse-large-b-cell-lymphoma-dlbcl-and-ongoing-ibrutinib-clinical-program.htm>
9. Richardson PG, Bensinger WI, Huff CA, et al. Ibrutinib alone or with dexamethasone for relapsed or relapsed and refractory multiple myeloma: phase 2 trial results. Br J Haematol. 2018;180(6):821-830.
10. Jones, J., Andritsos, L., Kreitman, ert al. Efficacy and Safety of the Bruton Tyrosine Kinase Inhibitor Ibrutinib in Patients with Hairy Cell Leukemia: Stage 1 Results of a Phase 2 Study. Blood. 2016;128(22):1215.
11. Tam CS, Anderson MA, Pott C, et al. Ibrutinib plus Venetoclax for the Treatment of Mantle-Cell Lymphoma. N Engl J Med. 2018;378(13):1211-1223.
12. Grommes C, Pastore A, Palaskas N, et al. Ibrutinib Unmasks Critical Role of Bruton Tyrosine Kinase in Primary CNS Lymphoma. Cancer Discov. 2017;7(9):1018-1029.
13. Shanafelt TD, Wang XV, Kay NE, et al. Ibrutinib-Rituximab or Chemoimmunotherapy for Chronic Lymphocytic Leukemia. N Engl J Med. 2019;381(5):432-443.
14. Woyach JA, Ruppert AS, Heerema NA, et al. Ibrutinib Regimens versus Chemoimmunotherapy in Older Patients with Untreated CLL. N Engl J Med. 2018;379(26):2517-2528.
15. Carpenter PA, Kang HJ, Yoo Kh, et al. Ibrutinib Treatment of Pediatric Chronic Graft-versus-Host Disease: Primary Results from the Phase 1/2 iMAGINE Study. Transplant Cell Ther. 2022 Aug 28:S2666-6367(22)01589-5. doi: 10.1016/j.jtct.2022.08.021.

Policy Implementation/Update:

Action and Summary of Changes	Date
Removed specialist requirement from renewal criteria	02/2025
Updated QL table to allow coverage of suspension in all indications	02/2024

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Following withdrawal of FDA approval: removed mantle cell lymphoma (MCL) from covered indications, added MCL in the not medically necessary uses section, removed marginal zone lymphoma (MZL) from experimental and investigational uses section, added marginal zone lymphoma (MZL) in the not medically necessary uses section, updated renewal section with standard policy renewal language requirements, updated supporting evidence, changed quantity limits for 140 mg tablets and capsules and 280 mg tablets to allow for MCL and MZL dosing, removed MCL and MZL from quantity limits table, removed 560 mg tablet formulation, changed initial authorization length from three to six months.	04/2023
Updated cGVHD for the age expansion for those aged 1 year or older. Added criteria for the new formulation approved (70mg/ml suspension) for use in pediatric patients. Added in related policy table.	10/2022
Removed initial criteria and moved MZL indication to investigational or not medically necessary uses section. Added supporting evidence for MCL indication and updated MCL investigational or not medically necessary uses section. Moved ibrutinib (Imbruvica) in combination with obinutuzumab in the setting of treatment naïve CLL/SLL to investigational or not medically necessary uses section.	01/2022
Addition of split-fill requirement. Included requirement the member has not progressed on a previous BTK inhibitor. Updated policy based on new indication in combination with rituximab for CLL/SLL as not medically necessary. Criteria for CLL/SLL updated to focus on diagnosis and mutation status over use in combination with other agents. Updated criteria for MCL and MZL to only be used as monotherapy. Removed toxicity renewal requirement and added disease stability renewal examples for GVHD patients.	06/2020
Updated criteria to policy format, specified combination therapy in CLL/SLL patients to be used in members without 17p deletion/TP53 mutation, addition of trial and failure of 140mg capsules prior to use of 140 mg or 280 mg tablets. In MCL, marginal zone lymphoma, and graft versus host disease, added more detail on type of prior therapy required. For Waldenström macroglobulinemia added use to be as monotherapy or with rituximab.	03/2019
Updated formatting, extended initial approval from 3 months to 6 months.	01/2018
Previous updates	08/2014 02/2015 04/2015 08/2017
Criteria created	02/2014

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP168

Description

Idelalisib (Zydelig) is an orally administered PI3Kδ kinase inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
idelalisib (Zydelig)	100 mg tablets	Relapsed Chronic Lymphocytic Leukemia	60 tablets/30 days
	150 mg tablets		

Initial Evaluation

- I. Idelalisib (Zydelig) 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. **Relapsed Chronic Lymphocytic Leukemia (CLL); AND**
 - i. Documentation of use of at least one prior therapy; **AND**
 - ii. Use is in combination with rituximab; **AND**
 - iii. Will not be used with any other oncology therapy
- II. Idelalisib (Zydelig) is considered investigational when used for all other conditions, including but not limited to:
 - A. Relapsed Small Lymphocytic Lymphoma (SLL)
 - B. Relapsed Follicular B-cell non-Hodgkin Lymphoma (FL)
 - C. Idelalisib as monotherapy for the treatment of relapsed or refractory CLL/SLL
 - D. Use as treatment naïve or first line therapy for any indication
 - E. In combination with other medications for any indication outside of dual therapy with rituximab for the indication of relapsed CLL
 - F. Marginal zone lymphoma
 - G. Lymphoplasmacytic lymphoma with or without Waldenstrom's macroglobulinemia
 - H. Immunoglobulin M (IgM) associated primary amyloidosis
 - I. Hodgkin Lymphoma
 - J. Acute Lymphoblastic Leukemia
 - K. 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. Member has exhibited improvement or stability of disease symptoms; **AND**
- IV. Member has a diagnosis of one of the following:
 - A. **Relapsed Chronic Lymphocytic Leukemia (CLL); AND**
 - 1. Use is in combination with rituximab

Supporting Evidence

- I. Safety and efficacy of idelalisib (Zydelig) has not been studied or established in the pediatric population.
- II. Treatment for CLL is a difficult to treat condition requiring consultation with an oncologist or hematologist.
- III. Idelalisib (Zydelig) was studied in a Phase III, randomized, double blind placebo controlled clinical trial in combination with rituximab in patients with relapsed chronic lymphocytic leukemia (CLL). Patients were given idelalisib (Zydelig) 150mg twice daily until disease progression or unacceptable toxicity. Nearly all patients had prior treatment with anti-CD20 monoclonal antibodies, and most patients also had prior treatment with bendamustine/rituximab, fludarabine/cyclophosphamide/rituximab, or rituximab monotherapy. Primary outcome was progression free survival and overall response rate with the median duration of response not reached.

Investigational or Not Medically Necessary Uses

- I. Relapsed Small Lymphocytic Lymphoma (SLL)
 - A. FDA accelerated approval was previously granted to idelalisib (Zydelig) for the treatment of SLL and FL based on results from a phase 2 clinical trial of patients with indolent Hodgkin lymphoma. Approval was contingent upon a positive confirmatory study, and this was not achieved. As the treatment landscape for FL and SLL has evolved, enrollment into the confirmatory study was an ongoing challenge. As a result, Gilead Sciences, Inc. notified the FDA of its decision to voluntarily withdraw these indications from the U.S. market.
 - B. Idelalisib (Zydelig) was studied in a Phase II, open label, single group clinical trial including patients with small lymphocytic leukemia (SLL) who had relapsed within six months following rituximab and an alkylating agent and had at least two prior treatments. The most common prior treatments included rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone, fludarabine/cyclophosphamide/rituximab, and bendamustine/rituximab. Primary outcome was overall response rate with the median duration of response of 11.9 months.
- II. Relapsed Follicular B-cell non-Hodgkin Lymphoma (FL)

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- A. FDA accelerated approval was previously granted to idelalisib (Zydelig) for the treatment of SLL and FL based on results from a phase 2 clinical trial of patients with indolent Hodgkin lymphoma. Approval was contingent upon a positive confirmatory study, and this was not achieved. As the treatment landscape for FL and SLL has evolved, enrollment into the confirmatory study was an ongoing challenge. As a result, Gilead Sciences, Inc. notified the FDA of its decision to voluntarily withdraw these indications from the U.S. market.
 - B. Idelalisib (Zydelig) was studied in a single-arm study including patients with follicular B-cell non-Hodgkins lymphoma who had relapsed within 6 months following treatment with rituximab and an alkylating agent and had at least two prior treatments. Patients were given idelalisib (Zydelig) 150mg twice daily until disease progression or toxicity. The most common prior treatments included rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone, rituximab/cyclophosphamide/vincristine/prednisone, and bendamustine/rituximab. Primary outcome was overall response rate with the median duration of response being not evaluable.
- III. Idelalisib as monotherapy for the treatment of relapsed or refractory CLL
- A. Idelalisib (Zydelig) was not found to be beneficial as monotherapy or as first line in patients with CLL. Label does not support use as monotherapy.
- IV. Idelalisib (Zydelig) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
- A. Use as treatment naïve or first line therapy for any indication
 - B. In combination with other medications for any indication outside of dual therapy with rituximab for the indication of relapsed CLL.
 - C. Marginal zone lymphoma
 - D. Lymphoplasmacytic lymphoma with or without Waldenstrom's macroglobulinemia
 - E. Immunoglobulin M (IgM) associated primary amyloidosis
 - F. Hodgkin Lymphoma
 - G. Acute Lymphoblastic Leukemia
 - H. Non-Small Cell Lung Cancer

References

1. Zydelig (idelalisib) [prescribing information]. Gilead Science, Inc, Foster City(CA). February 2022
2. ClinicalTrials.gov. A Randomized, Double-Blind, Placebo-Controlled Study of Idelalisib in Combination With Rituximab for Previously Treated Chronic Lymphocytic Leukemia (CLL). NCT01539512.
3. ClinicalTrials.gov. Efficacy and Safety Study of Idelalisib in Participants With Indolent B-Cell Non-Hodgkin Lymphomas. NCT01282424.
4. ClinicalTrials.gov. Efficacy and Safety Study of Idelalisib in Participants With Indolent B-Cell Non-Hodgkin Lymphomas. NCT01282424.
5. Gilead statement on Zydelig® U.S. indication for follicular lymphoma and small lymphocytic leukemia. News release. Gilead. January 18, 2022. <https://bit.ly/3qEeRnn>

Policy Implementation/Update:

Action and Summary of Changes	Date
Moved FL and SLL to E/I section following voluntary withdraw of these indications by the manufacturer.	03/2022
Policy updated to require use of one prior therapy for CLL; removed history of toxic epidermal necrolysis	02/2020

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Previous reviews	11/2014

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP123

Split Fill Management* (applies to olutasidenib [Rezlidhia] and ivosidenib [Tibsovo] only)

Description

Ivosidenib (Tibsovo) and olutasidenib (Rezlidhia) inhibit the isocitrate dehydrogenase 1 (IDH-1) enzyme, limiting the proliferation of the 2-HG oncometabolite, a competitive inhibitor of the normal metabolite, and promotes cell differentiation. Enasidenib (Idhifa) inhibits isocitrate dehydrogenase 2 (IDH-2), specifically targets IDH-2 variants mutant R140Q, R172S, and R172K to decrease 2-hydroxyglutarate (2-HG) levels and induce myeloid differentiation; thereby, reducing blast counts and increasing mature myeloid cell percentage. Vorasidenib (Vorango) is a dual inhibitor of both IDH-1 and IDH-2.

Length of Authorization

- Initial:
 - enasidenib (Idhifa): Six months
 - ivosidenib (Tibsovo) and olutasidenib (Rezlidhia): Six months; Split fill first three months
 - vorasidenib (Vorango): 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
enasidenib (Idhifa)	Acute myeloid leukemia, relapsed/refractory	50 mg tablets	30 tablets/30 days
		100 mg tablets	
ivosidenib (Tibsovo)	Acute myeloid leukemia, relapsed/refractory Acute myeloid leukemia, newly diagnosed Cholangiocarcinoma, advanced/metastatic Myelodysplastic syndromes, relapsed/refractory	250 mg capsule	60 capsules/30 days
olutasidenib (Rezlidhia)	Acute myeloid leukemia, relapsed/refractory	150 mg capsule	60 capsules/30 days
vorasidenib (Vorango)	Grade 2 IDH-mutant diffuse glioma (i.e., oligodendroglioma or astrocytoma)	40 mg tablet	30 tablets/30 days
		10 mg tablet	60 tablets/30 days

Initial Evaluation

- I. **Enasidenib (Idhifa), ivosidenib (Tibsovo), olutasidenib (Rezlidhia), and vorasidenib (Voranigo)** may be considered medically necessary when the following criteria are met:
 - A. Member is 18 years of age or older; **OR**
 - B. Member is 12 years of age or older; **AND**
 1. Request is for vorasidenib (Voranigo); **AND**
 - C. Medication is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
 - D. The member has not previously progressed on or after an isocitrate dehydrogenase (IDH) inhibitor [e.g., ivosidenib (Tibsovo), olutasidenib (Rezlidhia), enasidenib (Idhifa), vorasidenib (Voranigo)]; **AND**
 - E. A diagnosis of one of the following:
 1. **Relapsed or refractory acute myeloid leukemia (AML); AND**
 - a. Medication will not be used in combination with other oncologic agents (i.e., as monotherapy); **AND**
 - b. 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**
 - c. Presence of IDH-1 mutation as detected by an FDA-approved test is documented; **AND**
 - i. Request is for ivosidenib (Tibsovo) or olutasidenib (Rezlidhia); **OR**
 - d. Presence of IDH-2 mutation as detected by an FDA-approved test is documented; **AND**
 - i. Request is for enasidenib (Idhifa); **OR**
 2. **Newly diagnosed AML; AND**
 - i. Presence of IDH-1 mutation as detected by an FDA-approved test; **AND**
 - ii. Member is 75 years of age or older; **OR**
 - iii. Provider attests that the member has comorbidities that preclude intensive induction chemotherapy (e.g., baseline Eastern Cooperative Oncology Group performance status of ≥ 2 , severe cardiac or pulmonary disease, hepatic impairment with bilirubin >1.5 times the upper limit of normal, or creatine clearance <45 mL/min); **AND**
 - iv. Request is for ivosidenib (Tibsovo); **AND**
 - a. Treatment will not be used in combination with other oncologic agents (i.e., as monotherapy); **OR**
 - b. Treatment will be used in combination with injectable azacitidine; **OR**
 3. **Locally advanced or metastatic cholangiocarcinoma; AND**
 - i. Request is for ivosidenib (Tibsovo); **AND**
 - ii. Ivosidenib (Tibsovo) will not be used in combination with other oncologic agents (i.e., as monotherapy); **AND**
 - iii. Provider attests that the member is not a candidate for surgery (i.e., unresectable cholangiocarcinoma); **AND**
 - iv. Presence of IDH-1 mutation as detected by an FDA-approved test; **AND**
 - v. Member has had disease progression on, or after, at least one systemic therapy (e.g., gemcitabine, or 5-fluorouracil); **OR**
 4. **Relapsed or refractory myelodysplastic syndromes (MDS); AND**

- i. Request is for ivosidenib (Tibsovo); **AND**
 - ii. Ivosidenib (Tibsovo) will not be used in combination with other oncologic agents (i.e., as monotherapy); **AND**
 - iii. Documentation of IDH-1 mutation as detected by an FDA-approved test; **AND**
 - iv. Member has had disease progression on, or after, at least one systemic therapy (e.g., azacitidine, decitabine, cedazuridine, lenalidomide); **AND**
 - v. Attestation member is not eligible for currently enrolling clinical trials; **OR**
- 5. **IDH-mutant diffuse glioma; AND**
 - i. Request is for vorasidenib (Vorango); **AND**
 - ii. Documentation of an *IDH1* or *IDH2* mutation; **AND**
 - iii. Documentation member has Grade 2 astrocytoma (without 1p/19q codeletion); **OR**
 - a. Documentation member has Grade 2 oligodendroglioma (1p/19q-codeleted); **AND**
 - iv. Member has residual or recurrent tumor after surgery including biopsy, sub-total resection, or gross total resection; **AND**
 - v. Provider attestation of a Karnofsky performance status (KPS) of greater than or equal to 60 (i.e., able to live at home and care for most personal needs with varying amounts of assistance); **AND**
 - vi. Member has not undergone treatments with prior anticancer therapies (e.g., radiation therapy, chemotherapy) for the treatment of glioma.
- II. Enasidenib (Idhifa), ivosidenib (Tibsovo), olutasidenib (Rezlidhia), and/or vorasidenib (Vorango) are considered investigational when used for all other conditions, including but not limited to:
 - A. When used in combination with oncology therapies not specifically detailed above
 - B. Advanced cholangiocarcinoma without IDH-1 mutation
 - C. Chondrosarcomas
 - D. Myelodysplastic Syndrome (MDS) (therapies other than ivosidenib (Tibsovo))
 - E. Vorasidenib (Vorango) used in those with a poor performance status (Karnofsky PS <60)
 - F. Recurrent or Progressive Enhancing IDH-1 Mutant Glioma following treatment with other anti-cancer therapies (e.g., radiation therapy, chemotherapy)
 - G. Acute myeloid leukemia (newly diagnosed or relapsed/refractory)
 - H. IDH-mutant Grade 3 diffuse glioma

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., became independent of red blood cell and platelet transfusion, exhibited tumor response, no new T2 or FLAIR abnormalities, no new enhancement, stability of Karnofsky performance status)

Supporting Evidence

- I. Efficacy and safety of enasidenib (Idhifa), olutasidenib (Rezlidhia), and ivosidenib (Tibsovo) has not been studied in the pediatric population. Current FDA approvals for these agents are limited to adult members.
- II. Diagnosis and management of acute myeloid leukemia, myelodysplastic syndromes, cholangiocarcinomas, and gliomas require detailed clinical examination in combination with advanced testing such as MRI, EEG, and genetic screening (e.g., IDH-1 mutation). Given the complexities of diagnosis and treatment of these conditions, supervision of treatment by a hematologist or an oncologist is required.

Enasidenib (Idhifa):

- I. Enasidenib (Idhifa) was studied in a Phase I/II open-label, single-arm, multicenter, two-cohort clinical trial in patients who have a diagnosis of relapsed/refractory acute myeloid leukemia (AML) and IDH2 mutation. The study was conducted in 3 parts: (1) Phase 1 dose escalation, (2) Phase 1 expansion, and (3) Phase 2 expansion. Cohort 1 (dose-escalation): patients receiving enasidenib (Idhifa) 50mg to 650mg. Cohort 2 (Phase 1 & phase 2 expansion): patients receiving enasidenib (Idhifa) 100mg daily. The primary outcome measure of the study was to determine the safety and maximum tolerated dose (MTD) of enasidenib (Idhifa). In the phase I/II study, enasidenib (Idhifa) demonstrated that the MTD was not reached at doses of up to 650mg daily and 26.1% of all patients in the study had treatment-related serious adverse events.
- II. In the most recent Phase 2 expansion data, the secondary outcome measures were reported for patients who were taking enasidenib (Idhifa) 100mg daily, which included: a complete response (CR) of 20.1%, a median time to CR of 3.7 months, and the median duration of response for patients who achieved CR was 8.8 months.
- III. The National Comprehensive Cancer Network (NCCN) Guidelines preferred therapies for the treatment of recurrent/relapse AML include the following: clinical trial, systemic chemotherapy, or allogeneic hematopoietic stem cell transplant.

Ivosidenib (Tibsovo):

- I. Ivosidenib (Tibsovo) was studied in an open-label, single-arm, multicenter clinical trial in 174 adult patients with relapsed or refractory AML with an IDH-1 mutation. In this trial, the primary objectives were to assess the safety, maximum tolerated dose, and the recommended phase 2 dose of ivosidenib (Tibsovo) in patients with secondary, or later, relapse. Patients included in the trial had a relapse after stem-cell transplantation, had disease that was refractory to induction or reinduction chemotherapy, or had a relapse less than 12 months after initial therapy. Ivosidenib (Tibsovo) was approved in the setting of relapsed and refractory AML based on the following results: the rate of complete remission or complete remission with partial hematologic recovery was 30.4% (95% confidence interval [CI], 22.5 to 39.3), the rate of complete remission was 21.6% (95% CI, 14.7 to 29.8), and the overall response rate was 41.6% (95% CI, 32.9 to 50.8). Of note, 12% of the patients went on to stem cell transplantation following ivosidenib (Tibsovo) treatment and 15.1% of the patients died due to disease progression and complication of underlying disease (e.g., infection, respiratory failure, hemorrhage).
 - Ivosidenib (Tibsovo) was studied in an open-label, single-arm, multicenter clinical trial in 28 adult patients with newly diagnosed AML that have an IDH-1 mutation. In this trial, the eligible population included patients who were age 75 years or older or who had comorbidities that precluded the use of intensive induction chemotherapy (ECOG performance ≥ 2 , severe cardiac or pulmonary disease, hepatic impairment with bilirubin > 1.5 times the upper limit of normal, or CrCL < 45 mL/min). In this trial, the efficacy was determined by the rate of complete remission (CR) or

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complete remission with partial hematologic recovery (CRh), the duration of CR+CRh, and the rate of conversion from transfusion dependence to transfusion independence. Ivosidenib (Tibsovo) was granted FDA-approval as first-line therapy for AML patients with IDH-1 mutation, aged 75 years or above, or whose present comorbidities preclude the use of intensive induction chemotherapy. This approval was based on the following results: CR + CRh rate was 42.4% (95% confidence interval [CI], 25.5-60.8%) and 41.2% became independent of red blood cell (RBC) and platelet transfusion during any 56-day post-baseline period. Of note, 7% of the patients went on to stem cell transplantation following ivosidenib (Tibsovo) treatment.

- II. Efficacy and safety of combination ivosidenib (Tibsovo) and azacitidine was studied in a double-blind, randomized, placebo controlled, Phase 3 (AGILE) clinical trial. Adult participants (N=146) with newly diagnosed AML, confirmed IDH-1 mutations who were age 75 years or older or who had comorbidities that precluded the use of intensive induction chemotherapy were included in the study population. Patients were randomized 1:1 to ivosidenib (Tibsovo) plus azacitidine or placebo plus azacitidine. The trial ended early per an observation of the difference in number of deaths favoring ivosidenib (Tibsovo) and azacitidine arm – concluding the trial prior to enrolling the number needed for its power calculation. The primary outcome measure was progression event-survival reported as a hazard ratio of 0.33 (95% confidence interval [CI], 0.16 to 0.69; p= 0.002]. Median event-free survival was 0.03 months in both the treatment and placebo arms as more than half the patients in each arm did not have complete remission by week 24. Secondary endpoints included the rate of complete remission (CR) or complete remission with partial hematologic recovery (CRh) was 53% (95% CI, 41 to 65) in the treatment arm compared to 18% (95% CI, 10 to 28) in the placebo arm. Complete response (CR) was 47% (95% CI, 35 to 59) to 15% (95% CI, 8 to 25) respectively and the objective response rate was 62% (95% CI, 50 to 74) to 19% (95% CI, 11 to 30; p< 0.001). Median overall survival on the basis of 74 deaths was 24 months in the treatment arm (95% CI, 11.3 to 34.1) compared to 7.9 months (95% CI, 4.1 to 11.3) in the placebo arm HR 0.44; 95% CI, 0.27 to 0.73; P = 0.001). Together the combination ivosidenib (Tibsovo) + azacitidine provided a significantly better CR rate as compared to placebo + azacitidine. Additionally, combination therapy provided a favorable risk reduction in both PFS and OS indicating efficacy in the newly diagnosed AML population.
 - Though the AGILE study did not compare ivosidenib (Tibsovo) monotherapy to combination therapy with azacitidine indirect comparisons between ivosidenib (Tibsovo) monotherapy and ivosidenib (Tibsovo) + azacitidine combination therapy can be made. Combination therapy showed an increase in CR rates between the two trials [28.6% to 47% respectively]. Complete response (CR) is the first goal of AML induction chemotherapy. With a noted increase in reported CR rates in combination and monotherapy trials it can be assumed with moderate confidence that combination ivosidenib (Tibsovo) + azacitidine provides a clinically meaningful benefit as compared to monotherapy alone.
- III. Efficacy and safety of ivosidenib (Tibsovo) for the treatment of cholangiocarcinoma was evaluated in a double-blind, placebo-controlled, phase 3 (ClarIDHy) clinical trial. Adult participants (N=185), who had advanced or metastatic unresectable cholangiocarcinoma with documented IDH-1 mutation, and who had progressed on or after at least one systemic therapy consisting of gemcitabine or 5-fluorouracil were included. This trial included a one-way crossover allowing the patients randomized to placebo arm to crossover to receive ivosidenib (Tibsovo) upon progression. Although the crossover population was included for the calculation of overall survival (OS) data, primary outcome (progression-free survival (PFS)) only included initially

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randomized population (ITT analysis). After a median follow-up of 6.9 months, ivosidenib (Tibsovo) exhibited statistically significant improvement in PFS: 2.7 months versus 1.4 months for placebo arm (HR 0.37; 95% CI 0.25 to 0.54; $p < 0.0001$). Additionally median OS at data cut-off was 10.8 months (7.7, 17.6) with ivosidenib (Tibsovo) as compared to 9.7 months (4.8, 12.1) with placebo (HR 0.69; 95% CI 0.44, 1.10; $p = 0.06$). Although not statistically significant, in presence of significant primary outcome (PFS), the OS data provided indication of survival benefit with ivosidenib (Tibsovo). Additionally, treatment with ivosidenib (Tibsovo) also indicated improvement in quality of life parameters (QoL) upon comparing the patient answered questionnaires at cycle 2 of treatment versus cycle.

- During ClarIDHy clinical trial, 30% patients, who were on ivosidenib (Tibsovo), reported serious ($\geq$ grade 3) adverse reactions, which included hyperbilirubinaemia, jaundice cholestatic, ECG QT prolonged, and pleural effusion. No additional concerning safety signals were noted during this clinical trial when compared to previous trials for AML. Treatment related dose reduction rates were 3%, treatment discontinuation rate 6%, and dose interruption rate 29%, respectively. Among the 78 deaths (49 in the treatment arm) reported during the trial, none were ascribed as treatment-emergent.
- NCCN Guideline preferred first-line systemic therapies for the treatment of hepatobiliary cancer include surgical resection followed by adjuvant chemotherapy (e.g., capecitabine, 5-fluorouracil (5FU), cisplatin). For non-resectable metastatic biliary tract cancer, first-line gemcitabine in combination with cisplatin is preferred regimen (category 1). 5FU, FOLFOX, FOLFIRI may serve as subsequent-line therapies.

IV. Ivosidenib (Tibsovo) was studied in an ongoing Phase 1, open-label, single-arm, multicenter clinical trial of 18 adult patients with relapsed or refractory MDS with a susceptible IDH-1 mutation as detected by an FDA-approved test. Patients had a median age of 74 (range 61-84) and were treatment experienced, with chemotherapy (17% intensive chemotherapy vs 83% non-intensive chemotherapy). At the data cutoff, a CR of 38.9% was achieved with a median time to CR of 1.9 months (1.0 to 5.6 months). The median follow-up was 27.1 months (3.7 to 88.7 months) and median duration of exposure to ivosidenib (Tibsovo) was 8.3 months (3.3 to 78.8 months). Of the nine patients who were dependent on transfusions prior to initiation of therapy 6 (67%) became independent to RBC and platelet transfusions during the 56 days post-baseline.

- Fourteen patients (74%) were exposed to ivosidenib (Tibsovo) for at least 6 months and 8 patients (42%) were exposed for at least 1 year. Serious adverse reactions in $\geq 5\%$ included differentiation syndrome (11%), fatigue (5%), and rash (5%).
- NCCN guidelines currently recommend allo-HSCT, HMA-based therapies, high intensity chemo (induction), and clinical trial as standard therapies for MDS dependent on a patient's IPSS-R score. For those who are progress or fail to respond Tibsovo (ivosidenib) is guideline recommended as a treatment option (Category 2A) for those with IDH1 mutation.

Olutasidenib (Rezlidhia):

- I. The clinical program for olutasidenib (Rezlidhia) studied this agent as a monotherapy for the treatment of R/R AML. Participants in the clinical trial did not have previous treatment exposure to another IDH1 inhibitor (e.g., ivosidenib (Tibsovo)). At this time, the efficacy of olutasidenib (Rezlidhia) for patients, who have progressed on or after ivosidenib (Tibsovo) is unknown.
- II. Federal Drug Administration (FDA) approval of olutasidenib (Rezlidhia) was based on an ongoing open-label, single-arm, phase 1/ 2 clinical trial (Study 2102-HEM-101). Subjects (N= 147) with R/R AML and confirmed IDH1 mutation were given olutasidenib (Rezlidhia) 150 mg twice daily. The

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majority of patients had intermediate to poor cytogenetic risk and were experiencing first or second relapse with 31% patients being primary refractory. Twelve percent of patients had a history of HSCT. The efficacy of olutasidenib (Rezlidhia) was assessed based on the rate of complete remission (CR), complete remission with partial hematological recovery (CRh), and the duration of CR+CRh after a median follow-up duration of 10.2 months. Thirty-five percent of trial participants reported a combined CR + CRh with 32% achieving CR at the end of treatment exposure. Median duration of combined response was reported to be 25.9 months.

- III. Additionally, among the 86 patients who were dependent on red blood cell (RBC) and/or platelet transfusions at baseline, 29 (34%) became independent of RBC and platelet transfusions during any time in the 56-day post-baseline period. Of the 61 patients who were transfusion independent at baseline, 39 (64%) remained transfusion independent during any 56-day post-baseline period. Given the exchange between transfusion dependence and independence, the direct effect upon conversion to transfusion independence as a result of olutasidenib (Rezlidhia) remains uncertain.
- IV. Limitations of the clinical trial for olutasidenib (Rezlidhia) include the lack of a comparator, open-label study design, and lack of clinically meaningful outcomes. Although CR is an objective measure and can indicate an effective response to therapy, it remains shy of accurately predicting long-term prognosis and survival outcomes in AML. For newly diagnosed AML, CR following induction therapy has been associated with overall survival (OS) benefits. However, in the setting of R/R AML, morphologic and hematologic thresholds that define CR may be only indirect predictors of adequate response depth. Complete response (CR) remains an imperfect proxy for key long-term mortality outcomes. The quality of evidence is considered low due to the observational nature of the trial. Additionally, the efficacy of olutasidenib (Rezlidhia) in comparison with, or after, progression on ivosidenib (Tibsovo), remains unknown.
- V. During clinical trial, serious adverse events (AE) occurred in 25% of patients on therapy, which included differentiation syndrome (9%) and transaminitis (6%). The most common ($\geq 20\%$) AE included nausea (38%), fatigue (36%), edema (18%), arthralgia (28%), and leukocytosis (25%). Olutasidenib (Rezlidhia) therapy led to 32% dose interruptions due to AE, 11% dose reductions, and 8% permanent discontinuation of the therapy. Differentiation syndrome is a unique adverse effect of IDH inhibitors, which affected 16% of trial subjects within day one or 18 months of therapy and accounted for one death. The prescribing information for olutasidenib (Rezlidhia) includes boxed warnings regarding the risk of fatal differentiation syndrome and additional warning of hepatotoxicity. At this time, the real-world safety profile of olutasidenib (Rezlidhia) remains largely unknown.
- VI. The NCCN guidelines for the treatment of AML recommend olutasidenib (Rezlidhia) for the treatment of R/R AML (Category 2A recommendation). Olutasidenib (Rezlidhia) may be considered an alternative to ivosidenib (Tibsovo). The current clinical data for olutasidenib (Rezlidhia) does not provide evidence of the superiority of this drug as compared to ivosidenib (Tibsovo). At this time, weighing in the evidence of efficacy, safety, cost and net health benefits, ivosidenib (Tibsovo) and olutasidenib (Rezlidhia) may be considered comparable treatment options for R/R AML.

Vorasidenib (Vorango)

- I. Efficacy and safety of vorasidenib (Vorango) has not been studied in the pediatric population younger than 16 years old. However, there is access to vorasidenib (Vorango) via an expanded access program for those aged 12 years and older. FDA approval for this agent is in patients ≥ 12

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years old on the basis of additional population pharmacokinetic data demonstrating that age had no clinically meaningful effect on the pharmacokinetics of vorasidenib (Vorango).

- II. The INDIGO clinical program studied vorasidenib (Vorango) as a monotherapy for the treatment of Grade 2 IDH-mutant diffuse glioma (i.e., oligodendroglioma or astrocytoma). Participants in the clinical trial did not have any prior exposure to other anticancer agents for glioma.
- III. Vorasidenib (Vorango) was studied in a Phase 3, double-blind, placebo-controlled trial of 331 patients with IDH mutated residual or recurrent histologically confirmed Grade 2 oligodendroglioma or astrocytoma. All patients underwent surgery and had a measurable non-enhancing target lesion. Those with other prior anti-cancer treatments, including corticosteroids, were excluded.
 - Gliomas that have a mutation in *IDH1* or *IDH2* and an unbalanced translocation between chromosomes 1 and 19 (1p/19q-codeleted) are defined as oligodendrogliomas, whereas IDH-mutant gliomas without 1p/19q codeletion are defined as astrocytomas.
- IV. All participants in the INDIGO trial were required to have a Karnofsky performance status (KPS) score of at least 80 (0-100 with lower scores indicating greater disability). NCCN guidelines recommend those with a score greater than, or equal to, 60 as eligible for watchful waiting. A score of less than 60 indicates poor performance status where watchful waiting is not indicated. Use of vorasidenib (Vorango) outside of a population with good performance status has not been evaluated in clinical trials.
- V. The trial population had a slight male majority (1.3:1), with age ranging from 16 to 71 years (median ~40 years). More than half of patients (53%) had Karnofsky performance status of 100 at baseline, indicating no signs or symptoms of disease. Most patients were IDH1 positive (95%), while a minority were IDH2 positive (5%), and the most common IDH1 mutation was R132H (86%), oligodendroglioma (52%), and astrocytoma (48%). All patients had undergone brain tumor surgery previously, with 21.5% of the patients having undergone two or more tumor surgeries before enrollment. The median interval between the last glioma surgery and randomization was 2.4 years.
- VI. Patients were randomized 1:1 to vorasidenib (Vorango) or placebo. The trial ended early per an observation of vorasidenib (Vorango) demonstrating a benefit compared to placebo. The primary outcome measure was progression free survival (PFS) 27.7 months (17.0 to NE) vorasidenib (Vorango) compared to placebo 11.1 months (11.0 to 13.7) [HR 0.39 (95% CI, 0.27 to 0.56; P<0.001)]. Key secondary endpoints included time to next intervention (TTNI) which was not reached for the vorasidenib (Vorango) arm as compared to 17.8 months for placebo [HR 0.26 (95% CI, 0.15 to 0.43; P<0.001)].
- VII. The results of the INDIGO clinical trial showed vorasidenib (Vorango) significantly improved both imaging-based PFS, as compared with placebo, among patients who were considered to be candidates for watchful waiting. Progression free survival (PFS) and TTNI endpoints reported statistically significant differences in favor of vorasidenib (Vorango). Time to next intervention (TTNI) has not been reached for the vorasidenib (Vorango) group, though the proportion of patients not requiring next intervention at 24 months showed a stark difference between the treatment groups with 83.4% of patients in the vorasidenib (Vorango) arm not requiring next therapy as compared to 27% of the placebo arm. Additionally, overall response was also in favor of vorasidenib (Vorango). However, the number of patients achieving a partial or minor response were low and those achieving stable disease were comparable, 82.7% vs 88.3% in the vorasidineb (Vorango) and placebo groups respectively.
- VIII. Patients with diffuse LGG may have image-based progression (<25% increase of the lesion) but choose to continue therapy in the absence of symptoms of clinical deterioration. Continued use

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of vorasideneb (Vorango) in the presence of imaged-based progression may be clinically appropriate when clinical symptoms are stabilized. Clinical judgement should be exercised.

- Progression per RANO-LGG is defined as any of the following: (1) development of new lesions or increase of enhancement (radiological evidence of malignant transformation); (2) a 25% increase of the T2 or FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy, not attributable to radiation effect or to comorbid events; (3) definite clinical deterioration not attributable to other causes apart from the tumor, or decrease in corticosteroid dose; or (4) failure to return for evaluation because of death or deteriorating condition, unless caused by documented non-related disorders.
- The present RANO criteria for high-grade glioma that are recommended for a definition of clinical deterioration are a decrease in the Karnofsky performance score (KPS) from 100 or 90 to 70 or less, a decrease in KPS of at least 20 from 80 or less, or a decrease in KPS from any baseline to 50 or less, for at least 7 days. These definitions may be extrapolated to low-grade gliomas to assess the efficacy of therapy and progression to clinical deterioration.

Investigational or Not Medically Necessary Uses

- I. Enasidenib (Idhifa), ivosidenib (Tibsovo), olutasidenib (Rezlidhia), or vorasidenib (Vorango) used in combination with oncology therapies not specifically detailed above
 - A. Current clinical trial data leading to FDA approval are in the monotherapy setting [with the exception of ivosidenib (Tibsovo) in combination with azacitidine]. Safety and efficacy have not been established for specific combination regimens.
 - B. Olutasidenib (Rezlidhia) is currently being investigated in ongoing clinical trials in the settings of newly diagnosed AML, for the treatment of R/R AML in combination with hypomethylating agents (e.g., azacitidine), and for the treatment of myelodysplastic syndrome (MDS). However, clinical data from these trials are not available as of February 2023, and robust conclusions cannot be drawn with respect to potential of olutasidenib (Rezlidhia) as a treatment for these conditions.
 - C. Vorasidenib (Vorango) is currently being investigated in ongoing clinical trials in combination with pembrolizumab (Keytruda) for the treatment of recurrent or progressive Grade 2 or Grade 3 IDHm gliomas following prior treatment with chemotherapy, radiation or both. Additionally, vorasidenib (Vorango) in combination with temozolomide is under investigation for the treatment of Grade 2, 3 or 4 IDHm gliomas. However, trial results are not available as of October 2024 and safety and efficacy has not been established for use in these specific combination regimens.
- II. Advanced cholangiocarcinoma without IDH-1 mutation
 - A. Ivosidenib (Tibsovo) has received FDA approval in the setting of advanced cholangiocarcinoma with IDH-1 mutations. Efficacy and safety of this drug has not been established in the absence of IDH-1 mutations. Additionally, enasidenib (Idhifa) has not been sufficiently studied and is not FDA-approved for the treatment of cholangiocarcinoma.
- III. Chondrosarcomas
 - A. Clinical trials currently ongoing and limited to proof-of-concept.
- IV. Myelodysplastic Syndrome (MDS) (therapies other than ivosidenib (Tibsovo))

- A. Current clinical trials are being conducted in patients with myelodysplastic syndrome (MDS). There is currently insufficient evidence to support the safety and efficacy of enasidenib (Idhifa) and olutasidenib (Rezlidhia) for the treatment of MDS.
- V. Vorasidenib (Vorango) used in those with a poor performance status (Karnofsky PS <60)
 - A. All participants in the INDIGO trial were required to have a Karnofsky performance status score of at least 80 (0-100 with lower scores indicating greater disability). NCCN guidelines recommend those with a score greater than or equal to 60 as eligible for watchful waiting. A score of less than 60 indicates poor performance status where watchful waiting is not indicated per NCCN recommendations. Use of vorasidenib (Vorango) outside of a population with good performance status has not been evaluated in clinical trials.
- VI. Recurrent or Progressive Enhancing IDH-1 Mutant Glioma following treatment with other anti-cancer therapies
 - A. Clinical trials are being conducted in patients with grade 2 or 3 astrocytoma having received prior treatment with chemotherapy, radiation, or both. There is currently insufficient evidence to support the safety and efficacy of Vorasidenib (Vorango) for the treatment of recurrent or progressive disease following treatment with other anti-cancer therapies.
- VII. Acute myeloid leukemia (newly diagnosed or relapsed/refractory)
 - A. Clinical trials are being conducted in patients with newly diagnosed AML and R/R AML. There is currently insufficient evidence to support the safety and efficacy of Vorasidenib (Vorango) for the treatment of AML.
- VIII. IDH-mutant Grade 3 diffuse glioma
 - A. There is currently insufficient evidence to support the safety and efficacy of Vorasidenib (Vorango) for the treatment of Grade 3 diffuse gliomas. Use of vorasidenib (Vorango) outside of a population with Grade 2 disease has not been studied.

** 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. Tibsovo [prescribing information]. Cambridge, MA: Agios Pharmaceuticals, Inc.; October 2023.
2. Idhifa [package insert]. Cambridge, MA: Agios Pharmaceuticals & Celgene Corporation; December 2023.
3. DiNardo C, Stein EM, Botton S, et al. Durable Remissions with Ivosidenib in IDH1-mutated Relapsed or Refractory AML. *N Engl J Med*. 2018 June; 378:2386-2398. DOI: 10.1056/NEJMoa1716984
4. Roboz GJ, DiNardo CD, Stein EM, et al. Ivosidenib induces deep durable remission in patients with newly diagnosed IDH1-mutant acute myeloid leukemia. *Blood*. 2019; blood.2019002140. DOI:10.1182/blood.2019002140
5. Abou-Alfa GK, Macarulla T, Javle MM, et al. Ivosidenib in IDH1-mutant, chemotherapy-refractory cholangiocarcinoma (ClarIDHy): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Oncol*. 2020 Jun;21(6):796-807.
6. National Comprehensive Cancer Network. Hepatobiliary cancer (Version 4.2021). NCCN. August 26, 2021.
7. Montesinos P, Recher C, Vives S, et al. Ivosidenib and Azacitidine in IDH1-Mutated Acute Myeloid Leukemia. *N Engl J Med*. 2022;386(16):1519-1531. doi:10.1056/NEJMoa2117344.
8. Olutasidenib (Rezlidhia) Package Insert. Forma Therapeutics, December 2022.
9. Watts JM, Baer MR, et al. Olutasidenib alone or with azacitidine in IDH1-mutated acute myeloid leukemia and myelodysplastic syndrome: phase 1 results of a phase 1/2 trial. *Lancet Haematol*. 2022 Nov 9:S2352-3026(22)00292-7.

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10. De Botton S, Yee KWL, et al. Effect of olutasidenib (FT-2102) on complete remission in patients with relapsed/refractory (R/R) mIDH1 AML: Results from a planned interim analysis of a phase 2 clinical trial. ASCO 2021 conference abstract. J Clin Oncol, 2021 39 (15) 7006.
11. National Comprehensive Cancer Network. Acute Myeloid Leukemia. NCCN. V 3.2022; January 12, 2023. Accessed February 6, 2023. https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf.
12. National Comprehensive Cancer Network. Myelodysplastic Syndromes. NCCN. V 3.2023; November 10, 2023. Accessed December 8, 2023. https://www.nccn.org/professionals/physician_gls/pdf/mds.pdf
13. Mellinghoff IK, van den Bent MJ, Blumenthal DT, et al. Vorasidenib in IDH1- or IDH2-Mutant Low-Grade Glioma. *N Engl J Med*. 2023;389(7):589-601. doi:10.1056/NEJMoa2304194
14. National Comprehensive Cancer Network. Central Nervous System Cancers (Version 3.2024). NCCN. September 30, 2024. Accessed October 15, 2024. [cns.pdf \(nccn.org\)](https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf)
15. van den Bent MJ, Wefel JS, Schiff D, et al. Response assessment in neuro-oncology (a report of the RANO group): assessment of outcome in trials of diffuse low-grade gliomas. *Lancet Oncol*. 2011;12(6):583-593.
16. Voranigo. Package insert. Servier Pharmaceuticals LLC; 2024.
17. Classification and pathologic diagnosis of gliomas, glioneuronal tumors, and neuronal tumors. UpToDate. Wolters Kluwer Health, Inc. Riverwoods, IL. Accessed July 17, 2024. <https://www.uptodate.com/contents/classification-and-pathologic-diagnosis-of-gliomas-glioneuronal-tumors-and-neuronal-tumors>
18. Clinical features, diagnosis, and pathology of IDH-mutant, 1p/19q-codeleted oligodendrogliomas. UpToDate. Wolters Kluwer Health, Inc. Riverwoods, IL. Accessed July 17, 2024. <https://www.uptodate.com/contents/clinical-features-diagnosis-and-pathology-of-idh-mutant-1p19q-codeleted-oligodendrogliomas>
19. Treatment and prognosis of IDH-mutant astrocytomas in adults. UpToDate. Wolters Kluwer Health, Inc. Riverwoods, IL. Accessed July 17, 2024. <https://www.uptodate.com/contents/treatment-and-prognosis-of-idh-mutant-astrocytomas-in-adults>
20. Treatment and prognosis of IDH-mutant, 1p/19q-codeleted oligodendrogliomas in adults. UpToDate. Wolters Kluwer Health, Inc. Riverwoods, IL. Accessed July 17, 2024. <https://www.uptodate.com/contents/treatment-and-prognosis-of-idh-mutant-1p19q-codeleted-oligodendrogliomas-in-adults>

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)
decitabine/cedazuridine (Inqovi™)	Myelodysplastic Syndrome (MDS)
	Chronic myelomonocytic leukemia (CMML)
lenalidomide (Revlimid®), pomalidomide (Pomalyst®), thalidomide (Thalomid®)	Follicular lymphoma
	Marginal zone lymphoma
	Multiple myeloma
	Myelodysplastic syndromes
	Mantle cell lymphoma
	Erythema Nodosum Leprosum

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated to include vorasidenib (Voranigo) for the treatment of Grade 2 IDH-mutant oligodendrogliomas or astrocytomas. Updated E/I criteria to incorporate new to market medication.	11/2024
Update to include expanded indication for ivosidenib (Tibsovo) in R/R MDS and updated formatting of supporting evidence.	03/2024
Removed the requirement of contraindication/intolerance to Tibsovo prior to coverage of Rezlidhia for R/R AML. Current evidence of efficacy, safety, cost, and net health benefits indicates Tibsovo and Rezlidhia may be considered comparable treatment options for R/R AML.	03/2023
Update to include olutasidenib (Rezlidhia) for the new indication of R/R AML;	02/2023
Update to include expanded indication for ivosidenib (Tibsovo) plus azacitidine in newly diagnosed AML; updated supporting evidence; added related policies table.	11/2022
Update to include expanded indication for ivosidenib (Tibsovo) for cholangiocarcinoma; updated supporting evidence; added split fill requirement for Tibsovo.	10/2021

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Criteria update: To improve the clinical flow of the policy, the indication of relapse/refractory AML was separated from newly diagnosed AML. For clinical appropriateness and standard of practice, the requirement for both chemotherapy “AND” allogenic stem cell transplant for relapsed or refractory AML, was changed to an “OR;” therefore, either one prior regimen would satisfy that requirement. For the newly diagnosed AML diagnosis, additional information around comorbidities has been included in the policy to help better determine the comorbidities that may preclude newly diagnosed AML patients from intensive induction chemotherapy. Based on current clinical trials that are being conducted, myelodysplastic syndrome (MDS) has been added to the investigation/experimental section of this policy and supporting evidence has been updated to reflect the rationale for the addition. The supporting evidence in this whole policy has been updated to reflect the pivotal trials. The references section has been updated to include the pivotal trials and NCCN guideline for AML.	02/2020
Policy created. Tibsovo and Idhifa was combined into one policy.	12/2019

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP250

Description

Odevixibat (Bylvay) and maralixibat (Livmarli) are orally administered reversible ileal bile acid transporter (IBAT) inhibitors.

Length of Authorization

- Initial: Six months
- Renewal: Six months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
odevixibat (Bylvay)	Pruritis in patients three months of age and older with progressive familial intrahepatic cholestasis (PFIC)	200 mcg pellets 600 mcg pellets 400 mcg capsules 1200 mcg capsules	Monthly quantity to allow for a maximum of 120 mcg/kg/day (maximum of 6mg/day)
	Cholestatic pruritis in patients 12 months of age and older with Alagille Syndrome (ALGS)		Monthly quantity to allow for a maximum of 120 mcg/kg/day
maralixibat (Livmarli)	Cholestatic pruritis in patients 12 months of age and older with progressive familial intrahepatic cholestasis (PFIC)	19 mg/mL solution	Monthly quantity to allow for a maximum of 1,140 mcg/kg/day (maximum of 38 mg or 2 mL per day)
		10 mg tablets	60 tablets/30 days
		15 mg tablets	60 tablets/30 days
		20 mg tablets	60 tablets/30 days
		30 mg tablets	30 tablets/30 days
	Cholestatic pruritis in patients with Alagille Syndrome (ALGS) three months of age and older	9.5 mg/mL solution in 30mL bottle	Monthly quantity to allow for a maximum of 380 mcg/kg/day (maximum of 28.5 mg or 3 mL per day)
		10 mg tablets	30 tablets/30 days
		15 mg tablets	30 tablets/30 days
		20 mg tablets	30 tablets/30 days
		30 mg tablets	30 tablets/30 days

Initial Evaluation

- I. **Odevixibat (Bylvay)** and **maralixibat (Livmarli)** may be considered medically necessary when the following criteria are met:
 - A. Documentation of member's weight, measured within the past three months, is provided;

AND

- B. Medication is prescribed by, or in consultation with, a hepatologist or gastroenterologist;
AND
1. A diagnosis of **Progressive Familial Intrahepatic Cholestasis (PFIC)**; **AND**
 - i. Diagnosis is confirmed by a molecular genetic test; **AND**
 - ii. Member does not have PFIC type 2 with ABCB11 variants resulting in nonfunctional or absent bile salt export pump protein (BSEP) as confirmed by a molecular genetic test; **AND**
 - a. The request is for odevixibat (Bylvay); **AND**
 - i. Member is three months of age or older; **OR**
 - b. The request is for maralixibat (Livmarli); **AND**
 - i. Member is 12 months of age or older; **AND**
 - ii. Treatment with odevixibat (Bylvay) has been ineffective, not tolerated, or is contraindicated; **OR**
 2. A diagnosis of **Alagille Syndrome (ALGS)**; **AND**
 - i. Diagnosis is confirmed by a molecular genetic test; **OR**
 - a. Diagnosis is confirmed by evidence of bile duct paucity on liver biopsy; **AND**
 - b. Provider attestation that Alagille Syndrome (ALGS) is present in a first degree relative; **OR**
 - i. Provider attestation that member has presence of three or more clinical features of the disease (e.g., cholestasis, consistent cardiac, renal, ocular disease, butterfly vertebrae, or characteristic Alagille facies); **AND**
 - ii. The request is for maralixibat (Livmarli); **AND**
 - a. Member is three months of age and older; **OR**
 - iii. The request is for odevixibat (Bylvay); **AND**
 - a. Member is 12 months of age and older; **AND**
 - b. Treatment with maralixibat (Livmarli) has been ineffective, not tolerated, or is contraindicated; **AND**
- C. Provider attestation member has cholestasis including at least one of the following:
1. Total serum bile acids greater than three times the upper limit of normal for age; **OR**
 2. Conjugated bilirubin greater than 1 mg/dL; **OR**
 3. Unexplained fat-soluble vitamin deficiency; **OR**
 4. Gamma glutamyl transferase (GGT) greater than three times the upper limit of normal for age; **OR**
 5. Intractable pruritis explainable only by liver disease; **AND**
- D. Other causes of cholestasis have been ruled out (e.g., drug toxicity, hepatitis A, sclerosing cholangitis); **AND**
- E. Member does not have decompensated cirrhosis or prior hepatic decompensation events (e.g., variceal hemorrhage, ascites, hepatic encephalopathy); **AND**
- F. Provider attestation of presence of moderate to severe pruritis; **AND**
- G. Treatment with all the following has been ineffective, contraindicated, or not tolerated:
1. Ursodiol; **AND**
 2. Bile acid sequestrant (e.g., cholestyramine, colesevelam); **AND**
 3. Rifampin; **AND**
 4. Opioid antagonist (e.g., naltrexone); **AND**
 5. Serotonin inhibitor (e.g., sertraline, ondansetron)

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- II. Odevixibat (Bylvay) and maralixibat (Livmarli) are considered investigational when used for all other conditions, including but not limited to:
 - A. Benign recurrent intrahepatic cholestasis (BRIC) 1 and 2
 - B. Biliary Atresia
 - C. Primary sclerosing cholangitis (PBC)

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 pruritis, quality of sleep] **AND**
- IV. Documentation of member's weight, taken within past three months, is provided; **AND**
- V. Member has not had a liver transplant since the last prior authorization period; **AND**
- VI. Member has not progressed to decompensated cirrhosis or experience hepatic decompensation events (e.g., variceal hemorrhage, ascites, hepatic encephalopathy)

Supporting Evidence

Progressive familial intrahepatic cholestasis (PFIC)

- I. Progressive familial intrahepatic cholestasis (PFIC) is a group of rare genetic cholestatic diseases which may start early after birth or at a young age and may rapidly progress to end-stage disease. The disease is commonly classified as one of three PFIC 1-3 types depending on the genetic defect, although there may be up to six types. PFIC1 occurs due to mutations on the *ATP8B1* gene. This gene is also expressed in the small intestine, kidney, and pancreas, which explains certain extrahepatic manifestations (e.g., sensorineural deafness). PFIC2 occurs due to mutations on the *ABCB11* gene and PFIC3 is due to reduced expression of multidrug resistance MDR3, which is encoded by *ABCB4* gene.
- II. Patients often present with symptoms of cholestasis, growth retardation, increased serum bile acid (BA) blood and liver concentration, jaundice, and pruritis. Cholestasis is an impairment of bile formation and/or bile flow and is caused by absence of transport proteins in PFIC. The most sensitive test to confirm cholestasis is via elevations in fasting serum bile acids (normal levels depend on age but are usually <20 umol/L); however, this may not be readily available. Other biomarkers that can be used to confirm cholestasis are elevated gamma glutamyl transferase (GGT) levels (normal levels depend on age but are usually <200 IU/L) and conjugated/direct serum bilirubin levels (normal levels are usually less than 0.3 mg/dL). Additionally, cholestasis may be suspected in patients experiencing unexplained fat-soluble vitamin deficiency or intractable pruritis explainable only by liver disease.
- III. Pruritis is often described as unrelenting and debilitating, leading to cutaneous wounds and sleep disturbances and is one of the primary causes for surgical treatments and liver transplants. Pruritis is described as mild to moderate in intensity in patients with PFIC3 and as moderate to

severe in patients with PFIC1-2. If left untreated, the disease rapidly progresses to liver failure and is associated with early mortality.

- IV. Odevixibat (Bylvay) is FDA-approved for the treatment of pruritis associated with PFIC in patients three months of age and older. Age of PFIC onset varies by subtypes where PFIC1 and PFIC2 usually develop during infancy, and PFIC3 develops during late infancy to early adulthood. Symptoms of pruritis may present as early as three months of age.
- V. Maralixibat (Livmarli) is FDA-approved in PFIC in patients 12 months of age and older. Age of PFIC onset varies by subtypes where PFIC1 and PFIC2 usually develop during infancy, and PFIC3 develops during late infancy to early adulthood. Symptoms of pruritis may present as early as three months of age.
- VI. Progressive familial intrahepatic cholestasis (PFIC) should be considered in patients with cholestasis after ruling out more common causes such as biliary atresia, Alagille syndrome, alpha-1 antitrypsin deficiency, cystic fibrosis, drug toxicity, hepatitis A, sclerosing cholangitis, and extrahepatic bile duct obstruction. Diagnosis takes into account clinical, biochemical, radiological, and histological approaches. Genetic testing may be utilized for supporting a diagnosis of PFIC; however, the clinical phenotype is not always confirmed by genetic testing. This is likely due to other causative genes and/or non-coding regions of known PFIC genes that may contribute to disease manifestation. Approximately one-third of individuals with normal-GGT PFIC lack mutations in *ATP8B1* or *ABCB11* and mutations in *TJP2* explain all of the remaining patients. Additionally, in some patients only one allele of *ATP8B1* or *ABCB11* are detected, making it difficult to distinguish as disease-causing mutations or rare normal variants.
- VII. Odevixibat (Bylvay) and maralixibat (Livmarli) are not recommended in patients with BSEP3 variants (subpopulation within PFIC2). Pivotal trials excluded patients with BSEP3 variants as these patients lack a functional BSEP in canalicular member to export bile salts to bile for enterohepatic circulation via biliary excretion. Therefore, the pharmacological effects of odevixibat (Bylvay) and maralixibat (Livmarli) to inhibit the reabsorption of bile salts in the gastrointestinal tract cannot be expected.
- VIII. The majority of patients with PFIC receive liver transplantation before they reach adulthood. Intractable pruritis is a reason for evaluation for liver transplantation and placement on transplant list, regardless of the extent of direct liver involvement from PFIC. The majority of liver transplants in PFIC are considered successful with most patients alive without a need for re-transplantation. It is considered a curative treatment for the symptoms of pruritis. Therefore, odevixibat (Bylvay) and maralixibat (Livmarli) are not expected to be medically necessary in patients with liver transplants as these patients would likely be cured of pruritis.
- IX. Odevixibat (Bylvay) and maralixibat (Livmarli) were not studied in patients with decompensated cirrhosis or in patients with prior hepatic decompensation events (e.g., variceal hemorrhage, ascites, hepatic encephalopathy). Odevixibat (Bylvay) and maralixibat (Livmarli) should be permanently discontinued if patients progress to portal hypertension or experiences a hepatic decompensation event. Close monitoring and caution is warranted when initiating treatment in patients with liver disease.
- X. According to systematic reviews, around 80% of patients with PFIC have pruritis graded as severe and mild pruritis presentation is less common. PEDFIC1 pivotal trial population consisted of patients with a mean pruritis score of around 3 (a lot of scratching) on a scale from 0 (no scratching) to 4 (worst possible scratching). Additionally, PEDFIC1 inclusion criteria required

patients to have a history of significant pruritis and patients were included in the trial if the average scratching score was greater than or equal to 2 (medium scratching) in the 2 weeks prior to baseline. Similarly, in the MARCH-PFIC study the mean pruritis score was 2.9 with inclusion criteria requiring a score of ≥ 1.5 . Therefore, the value of odevixibat (Bylvay) and maralixibat (Livmarli) in patients with mild pruritis has not been established and the drugs may be medically necessary only in patients with history of significant scratching or medium scratching at baseline, consistent with moderate to severe pruritis presentation.

XI. Initial treatment of PFIC addresses nutritional problems and pruritis caused by cholestasis. Treatment response is often unpredictable; however, depending on the degree of pruritis and PFIC type, some patients may respond to pharmacological therapy with standard of care agents. There is lack of randomized controlled studies of standard of care agents in the treatment of PFIC; however, evidence related to pruritis is available from studies in other cholestatic disease states, retrospective PFIC cohort studies, and historical treatment experience with the drugs. Maralixibat (Livmarli) is a newer agent approved for the treatment of PFIC. There's no direct comparative evidence demonstrating superiority of one agent over the other. Trial of all standard of care agents including odevixibat (Bylvay) prior to maralixibat (Livmarli) is both a cost effective and clinically appropriate strategy as each drug exerts effects on pruritis via distinct therapeutic pathways and inefficacy with one or more agent(s) does not confer inefficacy with subsequent drugs.

- **Ursodiol** - commonly used as the first-line treatment option due to its anti-cholestatic properties which are exerted by improved hepatobiliary secretory function and reduced bile toxicity. It is the only medication that may affect liver disease progression and is recommended by the European Association for the Study of the Liver (EASL) guidelines as the initial pharmacological treatment in PFIC3. However, several rare disease organizations and expert reviews recommend ursodiol regardless of PFIC type. The effect of ursodiol on pruritis is an area that requires more research; however, several open-label and retrospective cohort studies note positive treatment response in pediatric patients with PFIC and other intrahepatic liver diseases (Narkewicz, 1998; Dinler, 1999; Wanty, 2004).
- Subsequent treatment options are aimed at reducing symptoms of pruritis. Pruritis can be a feature of any cholestatic disease, thus there are many treatment options available with variable evidence.
- **Bile acid sequestrants** - cholestyramine is FDA-approved for the treatment of pruritis associated with cholestasis in adults and is often used as one of the first-line treatment options for pediatric patients with pruritis associated with cholestasis. Despite a limited evidence base, cholestyramine is listed as a treatment option for PFIC by the Children's Liver Disease Foundation and is recommended first-line by EASL guidelines for the treatment of pruritis associated with cholestasis. The lack of evidence is largely because the agent entered widespread use before the era of evidence-based medicine. Additionally, colestipol and colesevelam have also been evaluated in the treatment of pruritis and are generally better tolerated than cholestyramine (Cies, 2007).
- **Rifampin** - is commonly used after treatment failure with ursodiol/cholestyramine and is recommended for the treatment of pruritis in pediatric patients with PFIC by

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EASL guidelines. Additionally, there are various reports in literature showing positive results on pruritis due to chronic cholestasis, including retrospective, case controlled, and prospective trials. One meta-analysis of five randomized prospective controlled trials in adults and children concluded that rifampin is safe and effective for the treatment of pruritis in patients with cholestasis associated with chronic liver diseases (Khurana, 2006).

- **Opioid antagonist** - naltrexone is recommended for the treatment of pruritis associated with cholestatic liver disease by the EASL guidelines as a subsequent option for patients failing cholestyramine and rifampin. Efficacy is supported by a meta-analysis which concluded that opioid antagonists significantly reduced cholestasis-related pruritis (Tandon 2007). Safety and efficacy of naltrexone in children is scarce; however, naltrexone can be safely used by pediatric patients with cholestatic liver disease and its use has been described in case reports and case series (Zellos, 2010; Mozer-Glassberg, 2011; Chang 2008).
- **Serotonin Inhibitors** - EASL guidelines recommended sertraline as a fourth-line treatment option for patients with cholestatic pruritis. Efficacy and safety are supported by one randomized double-blind, placebo-controlled study in patients with pruritis due to liver disease (Mayo, 2007) and one prospective multicenter study in children with refractory cholestatic pruritis related to PFIC and Alagille syndrome (Thebaut, 2017). Ondansetron has been studied in several cholestatic liver diseases with mixed results. One placebo-controlled trial studied intravenous ondansetron in adult patients with cholestatic pruritis and showed improvement in itch intensity by 50%. Another randomized, double-blind cross over study determined there was significant but moderate reduction in visual analogue scale (VAS) score when ondansetron was compared to placebo in patients with chronic liver disease. Another study showed that ondansetron therapy effectively reduced pruritis in 5 out of 13 patients, however, the reduction in itch intensity did not correlate to substantial decrease in objective scratching activity. A fourth clinical trial compared ondansetron to placebo and found no significant differences in pruritis scores or scratching activity (Ebhoon, 2023).

- XII. Odevixibat (Bylvay) was studied in PEDFIC1, a Phase 3, double-blind, placebo-controlled, randomized, 24-week trial followed by PEDFIC2, an open-label extension study. PEDFIC1 was conducted in 62 patients with pruritus, aged six months to 17 years, in patients with molecularly confirmed PFIC types 1 and 2. Patients received 40 mcg/kg or 120 mcg/kg odevixibat (Bylvay) dose and were allowed to continue on background treatment (e.g., ursodiol, rifampicin, antihistamines, naltrexone). The primary endpoint was the proportion of positive pruritis assessments (PPAs) as measured by the single-item observer-reported outcome instrument (ObsRo). The secondary endpoint was the change in serum BA from baseline. Both endpoints met statistical significance. Reduction in proportion of pruritis assessments to a score of 0 (no scratching) or 1 (little scratching) from baseline is also deemed clinically meaningful in a patient population refractory to standard of care. The safety data for odevixibat (Bylvay) is available for 69 patients. In PEDFIC1, adverse events (AEs) reported in $\geq 2\%$ of patients at a rate greater than placebo included diarrhea, increased bilirubin and transaminases, vomiting, abdominal pain, and fat-soluble vitamin deficiency. Drug related and liver related AEs occurred at a higher frequency

in odeixibat (Bylvay) treated patients than in placebo and included increased ALT (9.5% vs 5%), AST (7.1% vs 5%), bilirubin (9.5% vs 5%), and diarrhea (9.5% vs 5%). No differences in serious AEs were recorded in PEDFIC1. Interim analysis of PEDFIC2 trial show a similar trend with four additional patients reporting serious AEs of cholestasis, acute pancreatitis, splenomegaly, jaundice, hypophagia, and weight decrease. The rate of discontinuation due to adverse events was low.

- XIII. Maralixibat (Livmarli) was studied in MARCH-PFIC, a Phase 3, double-blind, placebo-controlled 26-week trial followed by an extension trial MARCH-ON. MARCH-PFIC was conducted in a total of 92 patients, aged ≥ 12 months and < 18 years of age. The median patient age was 4.8 years. The majority of patients enrolled had PFIC2 (n=31), followed by PFIC1 (n=13), PFIC3 (n=9), PFIC4 (n=7), and PFIC6 (n=4). Patients received maralixibat (Livmarli) up to 570 mcg/kg twice daily and were allowed to continue on background treatment (e.g., ursodiol, rifampicin, antihistamines, naltrexone). The primary endpoint was the mean change in the ItchRO (Obs) morning severity score in the PFIC2 cohort between baseline Week 15 through 26. The secondary endpoints included changes in serum BA levels and changes in pruritis and serum BA levels in other PFIC cohorts as well as responder analysis in all cohorts. The primary and secondary endpoints met statistical significance, except proportion of patients in the PFIC2 cohort that were considered ItchRO (Obs) responders. Clinically meaningful reductions in pruritis scores were observed in patients treated with maralixibat (Livmarli). Safety data is available for all 93 patients followed for 26-weeks as well as data from the long-term extension study. The most common AEs for maralixibat (Livmarli) vs placebo were diarrhea (57% vs 19%), abdominal pain (26% vs 13%), fat-soluble vitamin deficiency (28% vs 35%). The extension study did not report any new safety findings. Fourteen patients (16.5%) experienced a serious AE, with one patient (1.2%) experiencing an AE deemed treatment-related (increased blood bilirubin). Three patients experienced 4 AEs (including diarrhea, bilirubin increase, and ALT increase, and cirrhosis) which led to discontinuation. TEAEs led to death in 1 patient treated with maralixibat (respiratory infection), and was deemed not related to treatment, compared with 0 patients in the placebo group.

Alagille Syndrome (ALGS)

- I. Alagille Syndrome (ALGS) is a rare, genetic, autosomal dominant disorder, caused by mutations in the genes encoding jagged1 (JAG1) or neurogenic locus notch homolog protein 2 (NOTCH2), both involved in the Notch signaling pathway. It is a multisystem disorder affecting the liver, cardiovascular system, skeleton, face, and eyes. Phenotypic presentation of the disease is variable; however, complications can include cholestasis, pruritis, progressive liver disease, failure to thrive, and xanthomas, all of which lead to liver transplantation. Pruritis is the hallmark symptom of this disease and is thought to be caused by a buildup of pruritogens that accompany bile acids. Bile acid buildup occurs due to impaired development of bile ducts leading to bile duct paucity (reduction of interlobular bile ducts).
- II. Odeixibat (Bylvay) is FDA-approved for the treatment of cholestatic pruritis associated with ALGS in patients 12 months of age and older. Maralixibat (Livmarli) is FDA-approved for the treatment of ALGS in patients 3 months of age and older. The age of presentation ranges from 16 weeks to 10 years and most patients are diagnosed in the first year of life. The odeixibat (Bylvay) clinical trial program did not evaluate patients < 12 months of age; therefore, drug safety and efficacy in this population has not been established.

- III. Diagnosis of ALGS is based on a combination of clinical features of the disease, lab findings, imaging, genetic testing, and liver biopsy. Clinical features include hepatic manifestations such as chronic cholestasis and bile duct paucity, characteristic facial features (deep-set eyes and a flat nasal bridge), ophthalmic abnormalities, skeletal involvement, cardiovascular, and renal abnormalities. Cholestasis occurs in 87-100% of patients but may present as mild or not clinically identifiable in certain cases of ALGS. The most sensitive test to confirm cholestasis is via elevations in fasting serum bile acids (normal levels depend on age but are usually <20 umol/L); however, this may not be readily available. Other biomarkers that can be used to confirm cholestasis are elevated gamma glutamyl transferase (GGT) levels (normal levels depend on age but are usually < 200 IU/L) and conjugated/direct serum bilirubin levels (normal levels are usually less than 0.3 mg/dL). Additionally, cholestasis may be suspected in patients experiencing unexplained fat-soluble vitamin deficiency or intractable pruritis explainable only by liver disease. Patients affected with ALGS often present with multiple elevated biomarkers of cholestasis and peak values include bile acid levels > 100 times normal, total bilirubin > 20 mg/dL, and GGT > 2,000 U/L.
- IV. The molecular genetic test is considered confirmatory for ALGS syndrome. Majority of patients have mutations in JAG1 (94%) with only a small subset (<1%) having mutations in NOTCH2. Additionally, mutations that are variants of unknown significance can also cause ALGS. Genetic evaluation for JAG1 and NOTCH2 mutations is currently available on a commercial basis, though screening for NOTCH2 is limited to a small number of locations at this time.
- V. If patients are not screened for ALGS using a genetic test or if JAG1 or NOTCH2 mutations are not identified, patients may be diagnosed using a combination of clinical criteria, liver biopsy which screens for bile duct paucity, and presence of ALGS in first degree relatives. Bile duct paucity is one of the most common characteristics of ALGS and occurs in 90% of patients; however, it may not be present in many patients younger than six months of age and may not be present in mild disease presentation. Bile duct paucity is determined using a ratio of bile ducts to portal tracts of less than 0.5 in a liver biopsy with an adequate number (10) of portal tracts present. The normal number of bile ducts in a portal tract increases throughout the first years of life, reaching a normal ratio of nearly 2 by adolescence.
- VI. Diagnostic Criteria for Alagille Syndrome:

ALGS in a first degree relative	Paucity	JAG1 or NOTCH2 mutation*	Number of criteria needed**
Present or absent	Present	Identified	Any or no features
None (proband)	Present	Not identified	3 or more features
None (proband)	Absent or unknown	Not identified	4 or more features
None (proband)	Absent or unknown	Identified	1 or more features
Present	Present	Not identified	1 or more features
Present	Absent or unknown	Not identified	2 or more features
Present	Absent or unknown	Identified	Any or no features

*Not identified = not identified on mutation screening, or not screened for

** Major clinical criteria include cholestasis, consistent cardiac, renal, ocular disease, butterfly vertebrae, or characteristic Alagille facies of childhood or adulthood

- VII. Odevixibat (Bylvy) and maralixibat (Livmarli) were not studied in patients with decompensated cirrhosis or in patients with prior hepatic decompensation events (e.g., variceal hemorrhage, ascites, hepatic encephalopathy). Due to unknown safety and efficacy in this population,

odevixibat (Bylvay) and maralixibat (Livmarli) should be permanently discontinued if patients progress to portal hypertension or experience a hepatic decompensation event. Additionally, odevixibat (Bylvay) and maralixibat (Livmarli) are associated with causing liver test abnormalities and may or may not exacerbate liver injury in patients with severe liver disease (e.g., decompensated cirrhosis, portal hypertension). More studies are needed in this setting to confirm drug safety in significant liver disease.

- VIII. The majority of patients with ALGS receive liver transplantation before they reach adulthood. Intractable pruritis is a reason for evaluation for liver transplantation and placement on transplant list, regardless of the extent of direct liver involvement from ALGS. The majority of liver transplants in ALGS are considered successful with most patients alive without a need for re-transplantation. It is considered a curative treatment for the symptoms of pruritis. Therefore, odevixibat (Bylvay) and maralixibat (Livmarli) are not expected to be medically necessary in patients with liver transplants as these patients would likely be cured of pruritis.
- IX. Severe cholestatic pruritis occurs in up to 45% of patients with ALGS and has negative impacts on quality of life. Itching is often described as the most burdensome symptom of ALGS. According to one study evaluating the burden of ALGS and pruritis among 26 patients and 24 caregivers, 15% of patients experienced severe itching, 31% experienced moderate itching, 24% experienced mild itching, and 27% experienced very mild itching. Pivotal trials evaluating maralixibat (Livmarli) and odevixibat (Bylvay) studied patients with moderate to severe pruritis at baseline. The value of maralixibat (Livmarli) and odevixibat (Bylvay) in patients with mild pruritis has not been established and the drugs may be medically necessary only in patients with history of significant scratching or medium scratching at baseline, consistent with moderate to severe pruritis presentation.
- X. Treatment of ALGS is aimed at maintaining optimal nutrition, preventing fat-soluble vitamin deficiencies, addressing pruritis, improving bile flow, and treating any extrahepatic features. There are two FDA approved agents for pruritis associated with ALGS, which are maralixibat (Livmarli) and odevixibat (Bylvay) at this time; however, there are more agents that are commonly used off-label. For relief of pruritis unresponsive to antihistamines, ursodeoxycholic acid, rifampin, bile-acid sequestrants, naltrexone, and sertraline may be used. Antihistamines should not be exclusive therapy but can be dosed at night when pruritis interferes with sleep. Treatment response to pharmacological agents is often unpredictable; however, depending on the degree of pruritis, some experience relief of pruritis symptoms. Patients refractory to pharmacological therapy may undergo partial external biliary diversion or ileal exclusion surgery to remove excess bile prior to liver transplantation.
- XI. There is lack of robust studies of standard of care agents (ursodiol, bile acid sequestrants, rifampin, naltrexone, sertraline) in the treatment of ALGS; however, evidence related to pruritis is available from studies in other cholestatic disease states, retrospective and open-label ALGS studies, and historical treatment experience with the drugs. Maralixibat (Livmarli) is a newer agent approved for the treatment of ALGS. There is no direct comparative evidence demonstrating superiority of one agent over the other. Trial of all standard of care agents including maralixibat (Livmarli) prior to odevixibat (Bylvay) is both a cost effective and clinically appropriate strategy as each drug exerts effects on pruritis via distinct therapeutic pathways and inefficacy with one or more agent(s) does not confer inefficacy with subsequent drugs.

- **Ursodiol** - commonly used as the first-line treatment option due to its anti-cholestatic properties which are exerted by improved hepatobiliary secretory function and reduced bile toxicity. It is the only medication that may affect liver disease progression and is recommended by the European Association for the Study of the Liver (EASL) guidelines as the initial pharmacological treatment for cholestatic pruritis. Additionally, several rare disease organizations such as The Childhood Liver Disease Research Network and National Organization for Rare Disorders (NORD) and expert reviews recommend ursodiol as first line in patients with ALGS. The effect of ursodiol on pruritis is an area that requires more research; however, an open-label study, retrospective cohort study, and case reports note positive treatment response in pediatric patients with ALGS and other intrahepatic liver diseases (Kronsten, 2013; Narkewicz, 1998;).
- Subsequent treatment options are aimed at reducing symptoms of pruritis. Pruritis can be a feature of any cholestatic disease, thus there are many treatment options available with variable evidence.
- **Bile acid sequestrant** - cholestyramine is FDA-approved for the treatment of pruritis associated with cholestasis in adults and is often used as one of the first-line treatment options for pediatric patients with pruritis associated with cholestasis. Despite a limited evidence base, cholestyramine is listed as a treatment option for ALGS by The Childhood Liver Disease Research Network and NORD and is recommended first-line by EASL guidelines for the treatment of pruritis associated with cholestasis. There is additionally one retrospective study indicating efficacy in some patients. The lack of evidence is largely because the agent entered widespread use before the era of evidence-based medicine. Additionally, colestipol and colesevelam have also been evaluated in the treatment of pruritis and are generally better tolerated than cholestyramine (Cies, 2007; Kronsten, 2013).
- **Rifampin** - commonly used after treatment failure with ursodiol/cholestyramine and is recommended for the treatment of cholestatic pruritis by EASL guidelines, rare disease organizations, and expert reviews. Additionally, there are various reports in literature showing positive results on pruritis due to chronic cholestasis, including retrospective, case controlled, and prospective trials in other cholestatic diseases in children and adults. For example, one meta-analysis of five randomized prospective controlled trials in adults and children concluded that rifampin is safe and effective for treatment of pruritis in patients with cholestasis associated with chronic liver diseases (majority of patients had primary biliary cirrhosis). Additionally, one prospective study, one retrospective study, and cases reports are also available in patients with ALGS (Khurana, 2006; Yerushalmi, 1999; Kronsten, 2013).
- **Opioid antagonist** - naltrexone is recommended for the treatment of pruritis associated with cholestatic liver disease by the EASL guidelines as a subsequent option for patients failing cholestyramine and rifampin and is mentioned by expert reviews and rare disease organizations (NORD). Efficacy is supported by a meta-analysis which concluded that opioid antagonists significantly reduced cholestasis-related pruritis (Tandon, 2007). Safety and efficacy of naltrexone in children is scarce; however, naltrexone can be safely used by pediatric patients with cholestatic

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liver disease and its use has been described in a retrospective study, case reports and case series in patients with ALGS (Kronsten, 2013; Zellos, 2010; Mozer-Glassberg, 2011).

- **Serotonin Inhibitors** - EASL guidelines recommended sertraline as a fourth-line treatment option for patients with cholestatic pruritis. Efficacy and safety are supported by one randomized double-blind, placebo-controlled study in patients with pruritis due to liver disease (Mayo, 2007) and one prospective multicenter study in children with refractory cholestatic pruritis related to PFIC and Alagille syndrome (Thebaut, 2017). Ondansetron has been studied in several cholestatic liver diseases with mixed results. One placebo-controlled trial studied intravenous ondansetron in adult patients with cholestatic pruritis and showed improvement in itch intensity by 50%. Another randomized, double-blind cross over study determined there was significant but moderate reduction in visual analogue scale (VAS) score when ondansetron was compared to placebo in patients with chronic liver disease. Another study showed that ondansetron therapy effectively reduced pruritis in 5 out of 13 patients; however, the reduction in itch intensity did not correlate to substantial decrease in objective scratching activity. A fourth clinical trial compared ondansetron to placebo and found no significant differences in pruritis scores or scratching activity (Ebhoon, 2023).

- XII. Maralixibat (Livmarli) was studied in a pivotal Phase 2b, double-blind, placebo-controlled, randomized drug withdrawal (RWD) trial ICONIC, two randomized, double-blind, placebo-controlled Phase 2 trials ITCH and IMAGO, as well as ongoing open-label trial MERGE. The pivotal study included 31 pediatric patients (median age: 5.4 years) with ALGS (JAG1 mutation: 100%), native liver, elevated serum bile acids (mean: 283umol/L), and moderate to severe pruritis (mean weekly average ItchRO(Obs) score: 2.9). At baseline, patients were treated with standard of care agents (ursodeoxycholic acid: 81%; rifampin 74%; naltrexone: 3%; sertraline: 3%) that were continued during the trial. Patients were excluded if they had prior surgical interruption of the enterohepatic circulation, liver transplantation, and decompensated cirrhosis. The primary endpoints were the least square (LS) mean change in serum bile acid (sBA) levels and LS mean difference in pruritis severity as measured by the ItchRO(Obs) score between maralixibat (Livmarli) and placebo during the RWD period. Both endpoints met statistical significance and it was determined that there were substantial number of patients experiencing clinically meaningful change in pruritis scores while on treatment with maralixibat (Livmarli). Pooled safety data is available in 86 patients with ALGS with median duration of exposure of 32.3 months. Most common ($\geq 5\%$) any grade adverse events (AE) included diarrhea (55.8%), abdominal pain (53.5%), vomiting (40.7%), fat-soluble vitamin deficiency (25.6%), transaminases increased (18.6%), gastrointestinal bleeding (10.4%), bone fractures (9.3%), and nausea (8.1%). Three patients experienced vomiting as a serious AE requiring hospitalization or intravenous fluid administration. Treatment interruptions or dose reduction occurred in 5 (6%) patients due to diarrhea, abdominal pain, or vomiting. Seven (8.1%) patients discontinued due to ALT increase. There are no black box warnings or contraindications at this time. Warnings and precautions include liver test abnormalities, gastrointestinal adverse reactions, and fat-soluble vitamin deficiency.

- XIII. Odevixibat (Bylvay) was studied in one pivotal Phase 3, double-blind, placebo-controlled, trial ASSERT. The pivotal study included 52 pediatric patients (median age: 4.0 years) with ALGS (JAG1 mutation: 92%; NOTCH2 mutation 8%), native liver, elevated serum bile acids (mean: 240 umol/L), and moderate to severe pruritis (mean ObsRO score: 2.9). At baseline, patients were treated with standard of care agents (ursodeoxycholic acid: 89%; other anti-pruritis medication: 98%) that were continued during the trial. Other anti-pruritic drugs included rifampicin, naltrexone, antihistamines, steroids, gabapentin, ondansetron. Patients were excluded if they had prior surgical interruption of the enterohepatic circulation, liver transplantation, and decompensated cirrhosis. The primary endpoint was the least square (LS) mean change from baseline to month six in scratching score as measured by the PRUCISION observer-reported outcome (ObsRO) caregiver instrument. The secondary endpoints were changes from baseline in serum bile acids (sBA) and change from baseline in caregiver-reported sleep parameters. All endpoints met statistical significance and it was determined that there were substantial number of patients experiencing clinically meaningful change in pruritis scores while on treatment with odevixibat (Bylvay). Safety data is available from 35 patients treated with odevixibat (Bylvay) during the Phase 3 clinical trial ASSERT. Any treatment emergent adverse event rate was 74% in odevixibat (Bylvay) arm compared to 71% in placebo. Drug-related adverse events occurred more frequently in odevixibat (Bylvay) arm compared to placebo (23% vs 18%). Serious adverse events, and drug-related serious adverse events occurred at a similar frequency in both treatment arms. Most common drug related treatment emergent adverse events in the odevixibat (Bylvay) vs placebo arms, respectively, were diarrhea (11% vs 6%), vomiting (6% vs 0%), abdominal pain (3% vs 0%), hepatic enzyme increased (3% vs 1%), INR increased (3% vs 1%), frequent bowel movements (3% vs 0%), hematemesis (3% vs 0%), nausea (3% vs 0%), blood triglyceride increased (3% vs 0%), and weight decreased (3% vs 0%).

Investigational or Not Medically Necessary Uses

- I. Odevixibat (Bylvay) and maralixibat (Livmarli) have not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
- A. BRIC1 and BRIC2
 - i. BRIC1 and BRIC2 are milder versions of PFIC1 and PFIC2. BRIC1 and 2 occur on the same genes as PFIC1 and 2, respectively. However, cholestatic events are described as recurrent and unpredictable. Cholestatic episodes often last for a couple of weeks, vary in severity and duration and do not progress to liver failure. Therefore, there is uncertainty whether the duration of disease would offset treatment benefit. Further research and collection of evidence in patients with BRIC1 and BRIC2 is warranted at this time.
 - B. Biliary atresia
 - i. Odevixibat (Bylvay) is being studied in a Phase 3, double-blind, randomized controlled trial in patients with biliary atresia (NCT04336722). At this time, treatment with odevixibat (Bylvay) remains experimental and investigational.
 - ii. Maralixibat (Livmarli) is being studied in a Phase 2, double-blind, randomized controlled trial in patients with biliary atresia (NCT04524390). At this time, treatment with maralixibat (Livmarli) remains experimental and investigational.
 - C. Primary sclerosing cholangitis (PBC) – maralixibat (Livmarli)

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- i. PBC is a rare, chronic, progressive, autoimmune, cholestatic liver disease characterized by damage to intrahepatic bile ducts. Maralixibat (Livmarli) was studied in a phase 2, randomized, placebo-controlled trial in 66 patients aged 18-80 years with PBC and significant pruritis. The primary outcome was change in Adult Itch Reported Outcome (ItchRO) average weekly sum score (0, no itching; 70, maximum itching) from baseline to week 13/early termination (ET). Mean ItchRO weekly sum scores decreased from baseline to week 13/ET with maralixibat (Livmarli) (-26.5; 95% confidence interval [CI], -31.8, -21.2) and placebo (-23.4; 95% CI, -30.3, -16.4). The difference between groups was not significant (P = 0.48). Due to non-statistically significant results, maralixibat (Livmarli) was not associated with improvements in pruritis when compared to placebo and more studies are needed to evaluate this therapy in PBC.

Appendix

- I. Odevixibat (Bylvay) oral pellets are intended for use by patients weighing less than 19.5 kg and capsules are intended for use by patients weighing 19.5 kg or above.

II. **Odevixibat (Bylvay) Dosing Tables**

- A. Table 1: Recommended Dosage for **PFIC** (40mcg/kg/day)

Body weight (kg)	Total Daily Dose (mcg)
7.4 and below	200
7.5 to 12.4	400
12.5 to 17.4	600
17.5 to 25.4	800
25.5 to 35.4	1,200
35.5 to 45.4	1,600
45.5 to 55.4	2,000
55.5 and above	2,400

- B. Table 2: Recommended Dosage for **ALGS** (120mcg/kg/day)

Body weight (kg)	Total Daily Dose (mcg)
7.4 and below	600
7.5 to 12.4	1,200
12.5 to 17.4	1,800
17.5 to 25.4	2,400
25.5 to 35.4	3,600
35.5 to 45.4	4,800
45.5 to 55.4	6,000
55.5 and above	7,200

III. **Livmarli (Maralixibat) Dosing Tables**

- A. Livmarli tablets can be used for treatment of both ALGS and PFIC in patients weighing 25 kg and above who can swallow tablets. The use of Livmarli oral solution or Livmarli tablets should be based on the patient's weight and ability to swallow tablets

- B. Table 3: **LIVMARLI 9.5mg/mL Oral Solution** Administration for **ALGS**

Member weight (kg)	Days 1-7 (190 mcg/kg/day)	Beginning Day 8 (380 mcg/kg/day)	PA#1: quantity per 28-day	PA#2: quantity per 28-day	Renewal: quantity per

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	Volume QD (mL)	Volume QD (mL)	supply for month one (mL)	supply for month two through six (mL)	28-day supply (mL)
5 to 6	0.1	0.2	4.9	5.6	5.6
7 to 9	0.15	0.3	7.4	8.4	8.4
10 to 12	0.2	0.45	10.9	12.6	12.6
13 to 15	0.3	0.6	14.7	16.8	16.8
16 to 19	0.35	0.7	17.2	19.6	19.6
20 to 24	0.45	0.9	22.1	25.2	25.2
25 to 29	0.5	1	24.5	28	28
30 to 34	0.6	1.25	30.5	35	35
35 to 39	0.7	1.5	36.4	42	42
40 to 49	0.9	1.75	43.1	49	49
50 to 59	1	2.25	54.3	63	63
60 to 69	1.25	2.5	61.3	70	70
70 or higher	1.5	3	73.5	84	84

C. Table 4: **LIVMARLI** Tablets for Patients with **ALGS**:

Member Weight (kg)	Days 1 to 7 (190 mcg/kg QD)	Beginning Day 8 (380 mcg/kg QD)
Less than 25	Use Oral Solution	Use Oral Solution
25 to 32		10 mg
33 to 43		15 mg
44 to 65	10 mg	20 mg
66 or higher	15 mg	30 mg

**Select the appropriate product based on the patient's weight and ability to swallow tablets.*

D. Table 5: **LIVMARLI 19mg/mL Oral Solution** for Patients with **PFIC**:

- The recommended dosage is 570mcg/kg BID. The starting dose is 285mcg/kg QD, and should be increased to 285mcg/kg BID, 428 mcg/kg BID, and then to 570mcg/kg BID, as tolerated. The maximum daily dose should not exceed 38mg (2mL) per day and 40mg/day for Livmarli tablets.

Member Weight (kg)	285 mcg/kg (once daily titrated to twice daily)	428 mcg/kg (twice daily)	570 mcg/kg (twice daily as tolerated)
	19 mg/mL Solution (for PFIC) Volume per Dose (mL)		
5	0.1	0.1	0.15
6 to 7	0.1	0.15	0.2
8	0.1	0.2	0.25
9	0.15	0.2	0.25
10 to 12	0.15	0.25	0.3
13 to 15	0.2	0.3	0.4
16 to 19	0.25	0.4	0.5
20 to 24	0.3	0.5	0.6

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25 to 29	0.4	0.6	0.8
30 to 34	0.45	0.7	0.9
35 to 39	0.6	0.8	1
40 to 49	0.6	0.9	1
50 to 59	0.8	1	1
60 or higher	0.9	1	1

2. Table 6: LIVMARLI Tablets for Patients with PFIC

Member Weight (kg)	285 mcg/kg BID	428 mcg/kg BID	570 mcg/kg BID
Less than 25	Use Oral Solution	Use Oral Solution	Use Oral Solution
25 to 32			15 mg
33 to 43	10 mg	15 mg	20 mg
44 or higher	15 mg	20 mg	20 mg

*Select the appropriate product based on the patient's weight and ability to swallow tablets.

References

1. Livmarli. Package insert. Mirum Pharmaceuticals; April 2025.
2. Livmarli product dossier. Mirum Pharmaceuticals; March 2024.
3. Bylvay. Package insert. Ipsen Pharmaceuticals; June 2023.
4. ClinicalTrials.gov. NCT03566238 A double-blind, randomized, placebo-controlled, phase 3 study to demonstrate efficacy and safety of A4250 in children with progressive familial intrahepatic cholestasis types 1 and 2 (PEDFIC 1). June 2018. Available at <https://clinicaltrials.gov/ct2/show/NCT03566238>. Accessed 9/7/21.
5. ClinicalTrials.gov. NCT03659916 An open-label extension study to evaluate long-term efficacy and safety of A4250 in children with progressive familial intrahepatic cholestasis types 1 and 2 (PEDFIC 2). September 2018. Available at <https://clinicaltrials.gov/ct2/show/NCT03659916>. Accessed 9/7/21.
6. ClinicalTrials.gov NCT04674761 A Double-blind, randomized, placebo-controlled, Phase 3 study to investigate the efficacy and safety of odeixibat compared to placebo in Patients with Alagille Syndrome. April 2023. Available at: <https://clinicaltrials.gov/ct2/show/NCT04674761?term=NCT04674761&draw=2&rank=1>. Accessed 5/26/2023.
7. Baumann U., et al. "Effects of odeixibat on pruritus and bile acids in children with cholestatic liver disease: Phase 2 study." Clinics and research in hepatology and gastroenterology, vol. 45,5 101751. 26 Jun. 2021, doi:10.1016/j.clinre.2021.101751
8. Gunaydin M., et al. "Progressive familial intrahepatic cholestasis: diagnosis, management, and treatment." Hepatic medicine : evidence and research vol. 10 95-104. 10 Sep. 2018, doi:10.2147/HMER.S137209
9. Düll M., et al. Newer Approaches to the Management of Pruritus in Cholestatic Liver Disease. Curr Hepatology Rep 19, 86–95 (2020). <https://doi.org/10.1007/s11901-020-00517-x>
10. European Association for the Study of the Liver. "EASL Clinical Practice Guidelines: management of cholestatic liver diseases." Journal of hepatology vol. 51,2 (2009): 237-67. doi:10.1016/j.jhep.2009.04.009
11. Khurana., et al. "Rifampin is safe for treatment of pruritus due to chronic cholestasis: a meta-analysis of prospective randomized-controlled trials." Liver international : official journal of the International Association for the Study of the Liver vol. 26,8 (2006): 943-8. doi:10.1111/j.1478-3231.2006.01326.x
12. Thébaut., et al. "Sertraline as an Additional Treatment for Cholestatic Pruritus in Children." Journal of pediatric gastroenterology and nutrition vol. 64,3 (2017): 431-435. doi:10.1097/MPG.0000000000001385
13. Mayo, et al. "Sertraline as a first-line treatment for cholestatic pruritus." Hepatology (Baltimore, Md.) vol. 45,3 (2007): 666-74. doi:10.1002/hep.21553
14. Cies., et al. "Treatment of cholestatic pruritus in children." American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists vol. 64,11 (2007): 1157-62. doi:10.2146/ajhp060453
15. Zellos., et al. Use of oral naltrexone for severe pruritus due to cholestatic liver disease in children. J Pediatr Gastroenterol Nutr. 2010 Dec;51(6):787-9. doi: 10.1097/MPG.0b013e3181eb5ac0. PMID: 20948447.
16. Alagille syndrome Information for Physicians. The Childhood Liver Disease Research Network. Accessed May 26, 2023. <https://childrennetwork.org/For-Physicians/Alagille-Syndrome-Information-for-Physicians>

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17. Alagille syndrome. National Organization for Rare Disease. Updated 2020. Accessed May 26, 2023. <https://rarediseases.org/rare-diseases/alagille-syndrome/>
18. Kohut TJ, Gilbert MA, Loomes KM. Alagille Syndrome: A Focused Review on Clinical Features, Genetics, and Treatment. *Semin Liver Dis.* 2021;41(4):525-537. doi:10.1055/s-0041-1730951
19. Kronsten V, Fitzpatrick E, Baker A. Management of cholestatic pruritus in paediatric patients with alagille syndrome: the King's College Hospital experience. *J Pediatr Gastroenterol Nutr.* 2013;57(2):149-154. doi:10.1097/MPG.0b013e318297e384
20. Yerushalmi B, Sokol RJ, Narkewicz MR, Smith D, Karrer FM. Use of rifampin for severe pruritus in children with chronic cholestasis. *J Pediatr Gastroenterol Nutr.* 1999;29(4):442-447. doi:10.1097/00005176-199910000-00013
21. Narkewicz MR, Smith D, Gregory C, Lear JL, Osberg I, Sokol RJ. Effect of ursodeoxycholic acid therapy on hepatic function in children with intrahepatic cholestatic liver disease. *J Pediatr Gastroenterol Nutr.* 1998;26(1):49-55. doi:10.1097/00005176-199801000-00009
22. Mozer-Glassberg Y, Hojsak I, Zevit N, Shapiro R, Shamir R. Pruritus responsive to naltrexone in a patient with cholestatic liver disease. *Isr Med Assoc J.* 2011;13(2):111-112.
23. Ebhohon E, Chung RT. Systematic review: efficacy of therapies for cholestatic pruritus. *Therap Adv Gastroenterol.* 2023;16:17562848231172829. Published 2023 May 25. Doi:10.1177/17562848231172829
24. Alagille syndrome Information for Physicians. The Childhood Liver Disease Research Network. Accessed December 16, 2021. <https://childrennetwork.org/For-Physicians/Alagille-Syndrome-Information-for-Physicians>
25. Alagille syndrome. National Organization for Rare Disease. Updated 2020. Accessed December 16, 2021. <https://rarediseases.org/rare-diseases/alagille-syndrome/>
26. Shneider, Benjamin L et al. "Placebo-Controlled Randomized Trial of an Intestinal Bile Salt Transport Inhibitor for Pruritus in Alagille Syndrome." *Hepatology communications* vol. 2,10 1184-1198. 24 Sep. 2018, doi:10.1002/hep4.1244
27. Gonzales E, Hardikar W, Stormon M, et al. Efficacy and safety of maralixibat treatment in patients with Alagille syndrome and cholestatic pruritus (ICONIC): a randomised phase 2 study. *Lancet.* 2021;398(10311):1581-1592. doi:10.1016/S0140-6736(21)01256-3
28. Miethke A.G., Moukarzel A., Porta G., et al. Maralixibat in progressive familial intrahepatic cholestasis (MARCH-PFIC): a multicentre, randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet Gastroenterol Hepatol.* 2024. Doi: 10.1016/S2468-1253(24)00080-3

Related Policies

Currently there are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
Added Livmarli tablets to QL table. Updated criteria for Livmarli in PFIC to include coverage in pediatric patients 12 months of age or older. Updated appendix dosing tables.	10/2025
Added new strength of 19 mg/mL into QL table	09/2024
New policy titled Ileal Bile Acid Transporter Inhibitors created, combining previous maralixibat (Livmarli) and odeixibat (Bylvay) policies. New indication for maralixibat (Livmarli) added which is in the treatment of PFIC.	06/2024
Maralixibat (Livmarli) has been added as a step requirement for odeixibat (Bylvay) when the request is for ALGS.	11/2023
Original maralixibat (Livmarli) and odeixibat (Bylvay) policies renewal evaluation changed from 12 to six months; added ondansetron as an example of accepted medications in serotonin inhibitor class, updated supportive evidence sections, added related policies sections. New Alagille Syndrome indication added for odeixibat (Bylvay).	07/2023
Original maralixibat (Livmarli) policy created	02/2022
Original odeixibat (Bylvay) policy created	11/2021

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP315

Split Fill Management*

Description

Inavolisib (Itovebi) is an orally administered kinase inhibitor with activity against *PIK3CA* mutation.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
inavolisib (Itovebi)	Breast cancer, HR-positive, HER2-negative, <i>PIK3CA</i> mutated, endocrine-resistant, advanced or metastatic	3 mg tablets	28 tablets/28 days
		9 mg tablets	

Initial Evaluation

- I. **Inavolisib (Itovebi)** 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. Medication will be used in combination with fulvestrant (Faslodex) and palbociclib (Ibrance)*; **AND**
 - D. Medication will not be used in combination with any other oncology therapy except for fulvestrant (Faslodex) and palbociclib (Ibrance)*; **AND**
 - E. Member has not previously progressed on, or after, treatment with another cyclin-dependent kinase (CDK) 4/6 inhibitor [e.g., ribociclib (Kisqali), abemaciclib (Verzenio), palbociclib (Ibrance)] or *PIK3CA* active agent [e.g., alpelisib (Piqray), or capivasertib (Truqap)]; **AND**
 - F. Medication will be used as first-line therapy in the locally advanced or metastatic setting; **AND**
 - G. A diagnosis of **locally advanced or metastatic breast cancer** when the following are met:
 1. Breast cancer is hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative; **AND**
 2. Documentation of a *PIK3CA* mutation; **AND**
 3. Breast cancer is endocrine resistant, defined by disease progression on or within 12 months of completing adjuvant endocrine therapy (e.g., letrozole, anastrozole, exemestane, tamoxifen)

**Please note: medications notated with an asterisk may require additional review.*

- II. Inavolisib (Itovebi) is considered investigational when used for all other conditions, including but not limited to:
- A. As monotherapy for any indication
 - B. In combination with another cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor such as ribociclib (Kisqali) or abemaciclib (Verzenio)
 - C. Early breast cancer (neoadjuvant)
 - D. For the treatment of any other condition except for advanced or metastatic breast cancer
 - E. After progression on another Phosphoinositide 3-kinase (PI3K) inhibitor

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 disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread; **AND**
- IV. Medication will be used in combination with fulvestrant (Faslodex) and palbociclib (Ibrance)*; **AND**
- V. Medication will not be used in combination with any other oncology therapy except for fulvestrant (Faslodex) and palbociclib (Ibrance)*

**Please note: medications notated with an asterisk may require additional review.*

Supporting Evidence

- I. Inavolisib (Itovebi) is FDA approved in adults aged 18 years of age and older. Use in members younger than 18 years of age is not appropriate due to lack of established efficacy and safety.
- II. Given the complexities involved with the diagnosis, treatment approaches, and management of therapy for the indicated population, treatment with inavolisib (Itovebi) should be initiated by, or in consultation with, an oncologist.
- III. Inavolisib (Itovebi) is not FDA approved and has not been well studied in combination with oncolytic therapies other than fulvestrant (Faslodex) and palbociclib (Ibrance) at this time. Safety and efficacy as monotherapy or in combination with other regimens remains undetermined.
- IV. Current evidence is insufficient to determine if inavolisib (Itovebi), fulvestrant, and palbociclib (Ibrance) triple combination will remain efficacious when used after disease progression on a CDK 4/6 inhibitor in the early breast cancer or in metastatic breast cancer stages [ribociclib (Kisqali), abemaciclib (Verzenio), palbociclib (Ibrance)]. The INAVO120 inclusion criteria allowed use of prior CDK 4/6 inhibitors only if they were used in the early breast cancer stages and if progression occurred >12 months after CDK 4/6 inhibitor treatment completion. However, there were only four patients enrolled with this characteristic, precluding any definitive conclusions. There is a concern for cross-resistance between CDK 4/6 inhibitors which may render subsequent CDK 4/6 inhibitors ineffective. Benefits of continuing CDK 4/6 inhibitor beyond

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progression remain controversial and largely unknown at this time, necessitating high quality randomized controlled trials to explore this question. PostMONARCH, a Phase 3 study, and MAINTAIN, a Phase 2 study, evaluated this question, demonstrating improved progression free survival (PFS) when abemaciclib (Verzenio) or ribociclib (Kisqali) was used after progression on CDK 4/6 inhibitors; however, overall survival data remains immature, precluding any conclusions of the impact on overall survival. PALMIRA trial looked at continuing palbociclib (Ibrance) in the second line setting after previous progression on a palbociclib (Ibrance) based regimen. Results demonstrated that continuing palbociclib (Ibrance) did not significantly improve PFS compared to second-line endocrine therapy alone. ELAINE 3 and EMBER 3 are other trials evaluating this question, results of which are not available at this time. Currently, there is no high-quality prospective data to suggest that continuation of CDK 4/6 inhibitor beyond initial progression is effective and more high-quality data is required before this approach can be considered standard of care.

- V. Current evidence is insufficient to determine if (Itovebi), palbociclib (Ibrance), and fulvestrant triple regimen will remain efficacious after disease progression on another PI3K inhibitor such as alpelisib (Piqray), or an agent with activity against mutant *PIK3CA*, capivasertib (Truqap). Safety and efficacy of such use has not been established and remains experimental and investigational.
- VI. Treatment with inavolisib (Itovebi) in combination with palbociclib (Ibrance) and fulvestrant is appropriate when used as first-line in the locally advanced or metastatic setting as this is how inavolisib (Itovebi) was studied. Use in this setting is supported by the National Comprehensive Cancer Network (NCCN) breast cancer guidelines (category 1 recommendation). In the first-line setting, inavolisib (Itovebi) joins CDK 4/6 inhibitors ribociclib (Kisqali), abemaciclib (Verzenio), and palbociclib (Ibrance) in combination with aromatase inhibitors (AI) or fulvestrant. These are preferred first-line regimens for patients with HR-positive/HER2-negative, advanced or metastatic breast cancer irrespective of *PIK3CA* mutation and endocrine resistance. Inavolisib (Itovebi) has not been evaluated in second-line or beyond settings of advanced or metastatic breast cancer.
- VII. A diagnosis of locally advanced or metastatic breast cancer with presence of documented HR-positive/HER2-negative, *PIK3CA* mutated, endocrine resistant tumor profile is required as this is the only setting where inavolisib (Itovebi) has demonstrated adequate efficacy and safety. The pivotal trial, INAVO120, was a Phase 3, double-blind, placebo-controlled trial (N=325) studying patients with HR-positive/HER2-negative, locally advanced or metastatic breast cancer with progression during, or within, 12 months of completing adjuvant endocrine treatment with an aromatase inhibitor or tamoxifen, in combination with palbociclib (Ibrance) and fulvestrant. Patients who had progressed with CDK 4/6 inhibitors in the neoadjuvant or adjuvant setting more than 12 months after finishing CDK 4/6 inhibitor therapy were included in the study (n=4). Patients receiving prior systemic therapy for metastatic breast cancer and those with HbA1C >6% or diabetes were excluded. The majority of participants were female (98%), White (59%), with three or more organs with metastases (51%), secondary endocrine resistance (66%), and neoadjuvant or adjuvant chemotherapy (83%), and tamoxifen (48%) use. The primary efficacy outcome was median progression free survival (PFS) which was statistically significant and in favor of inavolisib (Itovebi), palbociclib (Ibrance), and fulvestrant (Faslodex) treatment arm (15 months) compared to placebo, palbociclib (Ibrance), and fulvestrant (Faslodex) (7.3 months), HR 0.43 (0.32-0.59), p<0.001. Median overall survival was immature at the time of data cut-off. The

overall quality of the data is low due to lack of mature OS data and use of surrogate outcomes (e.g., PFS) which do not have a strong correlation with improvements in OS in metastatic breast cancer space.

Investigational or Not Medically Necessary Uses

- I. Inavolisib (Itovebi) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. As monotherapy for any indication
 - i. There are currently no active Phase 2 or Phase 3 clinical trials studying inavolisib (Itovebi) as monotherapy for any indication
 - B. In combination with another cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitor such as ribociclib (Kisqali) or abemaciclib (Verzenio)
 - i. A Phase 1/2 trial (NCT03424005) is currently underway which is studying inavolisib (Itovebi) in combination with ribociclib (Kisqali) and abemaciclib (Verzenio) as well as other oncolytic therapies such as trastuzumab. Results are not available at this time. Study completion is estimated as 2028.
 - C. Early breast cancer (neoadjuvant)
 - i. A Phase 2 study is currently in process comparing neoadjuvant endocrine therapy in combination with trastuzumab, pertuzumab +/- inavolisib (Itovebi) in patients with early breast cancer. Results are not available at this time. Study completion is estimated in 2027.
 - D. For the treatment of any other condition except for advanced or metastatic breast cancer
 - i. A Phase 2 study is evaluating efficacy and safety of inavolisib (Itovebi) in combination with various oncolytic therapies in the treatment of ovarian cancer. Results are not available at this time. Study completion is estimated as 2028.
 - E. After progression on another Phosphoinositide 3-kinase (PI3K) inhibitor
 - i. There are currently no active Phase 2 or Phase 3 clinical trials studying inavolisib (Itovebi) in this setting.

** 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. Itovebi product dossier. Genentech, Inc; November 2024.
2. Itovebi. Package Insert. Genentech, Inc; November 2024.
3. National Comprehensive Cancer Network. Breast Cancer. NCCN. November 11, 2024. Accessed December 3, 2024. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
4. Turner NC, Im SA, Saura C, et al. Inavolisib-Based Therapy in *PIK3CA*-Mutated Advanced Breast Cancer. *N Engl J Med*. 2024;391(17):1584-1596. doi:10.1056/NEJMoa2404625
5. Mittal A, Molto Valiente C, Tamimi F, et al. Filling the Gap after CDK4/6 Inhibitors: Novel Endocrine and Biologic Treatment Options for Metastatic Hormone Receptor Positive Breast Cancer. *Cancers (Basel)*. 2023;15(7):2015. Published 2023 Mar 28. doi:10.3390/cancers15072015

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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
alpelisib (Piqray, Vijoice)	Breast cancer, HR+, HER2-, PIK3CA+, advanced or metastatic
Cyclin-Dependent Kinase (CDK) 4/6 Inhibitors	Breast cancer, HR+, HER2-, advanced or metastatic
elacestrant (Orserdu)	Breast cancer, HR+, HER2-, ESR1+, advanced or metastatic
capiwasertib (Truqap)	Breast cancer, HR+, HER2-, PIK3CA/AKT1/PTEN+, advanced or metastatic

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	02/2025

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP207

Description

inotersen (Tegsedi) is a subcutaneously administered antisense oligonucleotide inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

inotersen (Tegsedi)	Indication	Quantity Limit	DDID
284 mg/1.5 mL syringe	hereditary transthyretin-mediated amyloidosis	6 mL/28 days	204500

Initial Evaluation

- I. inotersen (Tegsedi) may be considered medically necessary when the following criteria are met:
 - A. Prescribed by or in consultation with a neurologist or cardiologist; **AND**
 - B. A diagnosis of hereditary transthyretin-mediated amyloidosis (hATTR) when the following are met:
 1. Age 18 years and older; **AND**
 2. Documented transthyretin variant (TTR mutation) by genotyping (e.g., V30M); **AND**
 3. Documented amyloid deposit by biopsy; **AND**
 4. Patient has a platelet count > 100 × 10⁹/L; **AND**
 5. Documentation of one of the following:
 - i. Patient has a baseline polyneuropathy disability (PND) score ≤ IIIb
 - ii. Patient has a baseline FAP Stage 1 or 2
 - iii. Patient has a baseline neuropathy impairment (NIS) score ≥ 10 and ≤ 130
 - AND**
 6. Presence of clinical signs and symptoms of the disease (e.g., peripheral sensorimotor polyneuropathy, autonomic neuropathy, motor disability, etc.); **AND**
 7. No prior liver transplant or anticipated liver transplant; **AND**
 8. New York Heart Association (NYHA) functional classification of <3; **AND**
 9. Does not have presence of known type 1 or type 2 diabetes mellitus; **AND**
 10. Does not have renal insufficiency (defined as CrCl <60 mL/min); **AND**
 11. Patient has tried and failed or has a contraindication to patisiran (Onpattro); **AND**
 12. Inotersen (Tegsedi) will not be used in combination with patisiran (Onpattro) or tafamidis meglumine (Vyndaqel)

- II. inotersen (Tegsedi) is considered investigational when used for all other conditions, including but not limited to:
 - A. Cardiac amyloidosis due to wild-type or mutant TTR

Renewal Evaluation

- I. Patient has previously received treatment with inotersen (Tegsedi); **AND**
- II. Documentation of one of the following:
 - A. Patient has a baseline polyneuropathy disability (PND) score $\leq$ IIIb; **OR**
 - B. Patient has a baseline FAP Stage 1 or 2; **OR**
 - C. Patient has a baseline neuropathy impairment (NIS) score $\geq$ 10 and $\leq$ 130
- AND**
- III. Documentation that the patient has experienced a positive clinical response to inotersen (Tegsedi) (e.g., improved neurologic impairment, motor function, quality of life, slowing of disease progression, etc.); **AND**
- IV. Inotersen (Tegsedi) will not be used in combination with patisiran (Onpattro) or tafamidis meglumine (Vyndaqel); **AND**
- V. Absence of unacceptable toxicity from the medication

Supporting Evidence

- I. In the pivotal NEURO-TTR trial leading to approval, inotersen (Tegsedi) was studied in adults with stage 1 (patient is ambulatory) or stage 2 (patient is ambulatory with assistance) hereditary transthyretin amyloidosis with polyneuropathy.
- II. Diagnosis of the hereditary form of ATTR requires demonstration of a TTR gene mutation. Although mass spectrometry can demonstrate a mass difference between wild-type and TTR protein variants in serum, it does not specify the site and kind of amino acid substitution in a number of disease-related TTR gene mutations; thus, DNA sequencing is usually required.
- III. Use of inotersen (Tegsedi) is contraindicated in patients with platelet count less than 100 x 10⁹/L, history of acute glomerulonephritis caused by inotersen (Tegsedi), or history of hypersensitivity reaction to inotersen (Tegsedi).
- IV. Patients with a PND score greater than IIIb (i.e. PND of IV) are confined to a wheelchair or bedridden. Patients with FAP stage 1 have unimpaired ambulation, stage 2 require assistance with ambulation, and FAP stage 3 patients are wheelchair bound or bedridden. As mentioned above, all patients included in the study were ambulatory. Patients included also had a baseline NIS score $\geq$ 10 and $\leq$ 130.
- V. Additional exclusion criteria in the NEURO-TTR trial consisted of prior liver transplant or anticipated liver transplant, New York Heart Association (NYHA) functional classification of <3 , presence of known type 1 or type 2 diabetes mellitus, and renal insufficiency (defined as CrCl <60 mL/min).
- VI. Inotersen (Tegsedi) carries two black box warnings related to potential for life-threatening thrombocytopenia and glomerulonephritis that may require immunosuppressive treatment and may result in dialysis. Tegsedi is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) program because of these risks. Patisiran (Onpattro) is also indicated and FDA approved for the polyneuropathy of hATTR in adults and provides a more favorable safety profile. Onpattro efficacy was evaluated in a randomized, double-blind,

placebo-controlled trial in adults with polyneuropathy caused by hATTR amyloidosis. Onpattro met its primary endpoint of change from baseline to Month 18 in the modified Neuropathy Impairment Score +7 (mNIS+7).

- VII. Use of inotersen (Tegsedi) in combination with other therapies for hATTR (e.g., patisiran (Onpattro) or tafamidis meglumine (Vyndaqel) has not been studied.

Investigational or Not Medically Necessary Uses

- I. Cardiac amyloidosis due to wild-type or mutant TTR
 - A. Pivotal trials leading to FDA approval were specifically in the hereditary transthyretin-mediated amyloidosis setting. Wild-type TTR is not considered hereditary. Inotersen (Tegsedi) in this setting is under investigation, trials have not yet started recruiting.

References

1. Tegsedi [Prescribing Information]. Carlsbad, CA: Ionis Therapeutics, Inc., 2018.
2. Adams D, Gonzalez-Duarte A, O'Riordan WD, et al. Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis. NEJM. 2018;379(1):11-21. doi:10.1056/NEJMoa1716153.
3. Buxbaum J. Oligonucleotide Drugs for Transthyretin Amyloidosis. NEJM. 2018;379(1):82-85. doi:10.1056/NEJMe1805499.
4. Gonzalez-Duarte A, Adams D, O'Riordan W, et al. Changes in Neuropathy Stage in Patients with Hereditary Transthyretin-Mediated Amyloidosis Following Treatment with Patisiran, an Investigational RNAi Therapeutic: An Analysis from the Phase 3 APOLLO Study. Available at: http://www.alnylam.com/wp-content/uploads/2018/03/5.-APOLLO-PND-FAP_FINAL.pdf.
5. Center for Drug Evaluation and Research. Tegsedi (inotersen) Summary Review. Application Number: 211172Orig1s000. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/211172Orig1s000SumR.pdf
6. Benson MD, Waddington-cruz M, Berk JL, et al. Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis. N Engl J Med. 2018;379(1):22-31.
7. Coelho T, Ericzon B, Falk R, et al. A Guide to Transthyretin Amyloidosis. Available at: <http://www.amyloidosis.org/wp-content/uploads/2017/05/2017-ATTR-guide.pdf>.
8. Ando Y, Coelho T, Berk JL, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. Orphanet J Rare Dis. 2013;8(1):1-18. doi:10.1186/1750-1172-8-31.

Policy Implementation/Update:

Date Created	January 2019
Date Effective	February 2019
Last Updated	January 2019
Last Reviewed	01/2019

Action and Summary of Changes	Date
Criteria created	01/2019

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP238

Description

Interferon Gamma-1B (Actimmune®) is a subcutaneously administered medication which works through an unknown mechanism of action after binding to the cell's surface. The three major groups of interferons (alpha, beta, gamma) all have overlapping properties. Interferon gamma binds to a different surface receptor than alpha and beta and is considered a Type 2 interferon. Specific effects from using interferon gamma include activation of natural killer (NK) cells, enhancement of the oxidative metabolism of macrophages, and antibody dependent cellular cytotoxicity (ADCC).

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
Interferon Gamma-1B (Actimmune®)	100mcg (2 million IU)/0.5ml vial	Severe Malignant Osteopetrosis (SMO); Chronic Granulomatous Disease (CGD)	BSA* over 0.5 m ² : 50mcg/m ² Three times weekly
			BSA* equal to or less than 0.5m ² : 1.5mg/kg/dose Three times weekly

*maximum dose: 50mcg/m² Body surface area (BSA)

Initial Evaluation

- I. **Interferon Gamma-1B (Actimmune)** may be considered medically necessary when the following criteria are met:
 - A. Medication is prescribed by, or in consultation with, a specialist (e.g., endocrinologist, immunologist, geneticist); **AND**
 - B. Member will not use this medication in combination with another biologic or other non-biologic specialty medication; **AND**
 - C. A diagnosis of one of the following:
 1. **Chronic granulomatous disease (CGD); AND**
 - i. Attestation the member has a confirmed molecular genetic test and/or by neutrophil-functioning test confirming diagnosis; **AND**
 - ii. Member is on continuous daily antibiotic therapy (e.g., sulfamethoxazole-trimethoprim) and antifungal therapy (e.g., itraconazole) for infection prophylaxis; **OR**
 2. **Severe Malignant Osteopetrosis (SMO); AND**

- i. Member has confirmed genetic testing identifying a mutation linked to severe, infantile, malignant osteopetrosis; **AND**
 - ii. Member has had a radiographic (x-ray) image confirming skeletal features related to osteopetrosis
- II. **Interferon Gamma-1B (Actimmune)** is considered investigational when used for all other conditions, including but not limited to:
 - A. Atopic Dermatitis
 - B. Renal Cell Carcinoma
 - C. Mycosis Fungoides/Sezary Syndrome
 - D. Friedreich's Ataxia
 - E. Noninfantile osteopetrosis (conditions outside of severe, infantile (SMO))

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 primary infections, stabilization of platelet or hemoglobin counts, decrease/stabilization in optic atrophy]

Supporting Evidence

- I. Chronic granulomatous disease (CGD) is a rare and inherited primary immune deficiency disorder affecting white blood cells and the body's ability to resist infections caused by certain types of bacterial and fungal species. Overtime, this causes the body to develop chronic inflammation of the tissues, known as granulomas, which can be widely distributed over the body and have the potential to develop into life-threatening infections of the skin, lungs, and bones.
- II. In CGD, there is a genetic mutation in one of five genes that cause a defect in an enzyme called phagocyte NADPH oxidase; this enzyme is used by certain white blood cells in the cell killing process of certain bacteria and fungi. Usually this is routinely done in children with a family history of CGD or will be performed in children who have symptoms that match the symptom profile. The first testing done is either the DHR (dihydrorhodamine) (flow cytometry test) or the NBT (nitroblue tetrazolium) test. Both work in a similar manner and check to see if the patient's blood cells are producing the enzyme NADPH oxidase. The DHR test will change the fluorescein of dihydrorhodamine and that can be detected by the flow cytometer; the NBT test will change the color of the cell itself and this can be then seen under a microscope. Once a positive result is found on either test, genetic testing is done to assess which mutation the patient has, as the type of mutation can impact how the disease might present and when it might present (i.e. later in life in certain carriers; more autoimmune manifestations like Raynaud's, oral ulcers) and this genetic testing is important for carriers to know the genetic potential of passing to any children they might have.

- III. As CGD is a genetic disease, the first symptoms are usually noticed during infancy or childhood, though cases have been reported not diagnosed until the early teens or even adulthood. Standard of care consists of continuous antibiotic therapy to help prevent infections, such as trimethoprim/sulfamethoxazole to prevent bacterial infections and itraconazole for anti-fungal protection. Corticosteroids are also helpful for treating granulomatous complications and to bring down inflammation. The only potential cure for CGD is a bone marrow transplant which has been successful in some patients. Interferon gamma-1B has been shown in vitro and in vivo to correct parts of the damage to the oxidative metabolic system of the cells and therefore, help improvement their microbe killing potential (ability to kills bacteria, fungi, and viruses).
- IV. Actimmune was approved by the FDA for use in CGD following a randomized, double blind, placebo-controlled trial to determine if Actimmune used subcutaneously (SQ) three times a week could decrease the incidence of serious infectious episodes and improve existing infectious and inflammatory conditions of those enrolled in the study with CGD. A hundred and twenty-eight patients were enrolled, of those enrolled all had different methods of genetic inheritance and most patients were on prophylactic antibiotics. Patients had a median age of 14.6 years but ranged from 1-44 years. The study itself ended early following demonstration of a highly statistically significant benefit of Actimmune compared to placebo, ($p=0.0036$) for the primary endpoint of the study, time to a serious infection. There was a 67% reduction in relative risk of serious infections in those receiving Actimmune to place ($N=63$ to $N=65$, respectively) and additional evidence for the treatment benefit of Actimmune showed a twofold reduction in the number of primary infections (30, placebo and 14, Actimmune; $p=0.002$).
- V. Osteopetrosis is a genetic disease marked by increased bone density from a defect in the bone being reabsorbed into the cells by osteoclasts. This leads to bone being made up/built of a defective structure causing them to be brittle and likely to fracture; this often leads to misclassification under a type of bone fragility. Three types of osteopetrosis exist and are differentiated based on the genetic mutation. The autosomal recessive form, severe malignant osteopetrosis (SMO) [sometimes referred to as malignant infantile osteoporosis (MIOP)], is apparent soon after birth and shortens life expectancy, usually leading to death within the first decade of life, affecting about 1 in 250,000 people. Genetic testing is recommended once an x-ray diagnosis is established because it can separate the different forms of osteopetrosis and provide meaningful effect on management strategies.
- VI. Additional types of osteopetrosis are Autosomal Dominant (aka Albers-Schonberg disease or ADO), Intermediate Autosomal (IAO), and Adult Delayed-Onset. ADO is the most common and usually has an onset in adolescence or adulthood with long bone involvement leading to fractures along these bones such as the femur and ulnar. Other common symptoms include hip osteoarthritis, scoliosis, osteomyelitis of the jawbone, and infection within the bone itself. IAO onsets in childhood and can cause skeletal changes as well as visual impairment from optic nerve compression but does not change life expectancy. Adult Delayed-Onset is a milder type of ADO with normal bone structure at birth and people tend to remain asymptomatic. In this later state, bone mass will increase with age, and usually osteomyelitis of the jaw is first symptom, followed by bone pain, fractures, back pain (along vertebra), and degenerative arthritis.
- VII. The only established cure for SMO is a hematopoietic stem cell transplant (HSCT) which allows restoration of bone resorption by the donor osteoclasts. Certain genetic mutations within SMO will not benefit from the transplant (those with the *RANKL* gene) and a large number of patients

develop some sort of progression neurodegeneration which is not helped with a HSCT. For patients where an HSCT is not appropriate, corticosteroids may be considered, but there is not strong evidence to support their routine use. Interferon Gamma-1B was approved to help delay disease progression along with dietary and nutrition support. Interferon Gamma-1B is not indicated for the other types of osteopetrosis as ADO, IAO, or Adult-Delayed; as they can all be managed by things such as calcitriol, to help stimulate osteoclasts, erythropoietin, or corticosteroids.

- VIII. Actimmune received FDA approval for SMO following a randomized, controlled trial in patients with SMO who received doses of Actimmune (three times weekly) + calcitriol or just calcitriol alone. The study only enrolled 16 patients with n=11 receiving study regime and n=5 receiving the controller alone; patients were a mean age of 1.5 years (1month-8 years). The study evaluated time to disease progression and treatment failure was considered to be disease progression based on four outcomes: 1. Death; 2. Significant reductions in hemoglobin or platelet counts; 3. Serious bacterial infections requiring antibiotics; or 4. A 50dB decrease in hearing or progressive optic atrophy. The median time to disease progression was significantly delayed in the study arm versus control arm. However, this was based on the observed data as time to progression in the treatment arm was at least 165 days versus 65 days in the calcitriol alone arm.
- IX. Actimmune has a similar safety profile as the other interferons. The most common adverse reactions include fever, headache, chills, myalgia, or fatigue. It is recommended to have baseline hematology, blood chemistries, and urinalysis prior to starting and at 3-month intervals once using the medication. It is further recommended for severe reactions, to dose reduce by 50% or discontinue the therapy until the ADE resolves. Examples of these serious adverse reactions are neutropenia, thrombocytopenia, elevations of AST/ALT, decreased mental status, and gait disturbances.
- X. As each of these FDA label indications are an involved genetic disorder, the request should be coming from a specialist with understanding of the disease state.

Investigational or Not Medically Necessary Uses

- I. Interferon Gamma-1B (Actimmune) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Atopic Dermatitis (AD)
 - i. In 2000, a randomized, placebo-controlled study looked at the therapeutic effect of two different dosages of interferon gamma for AD for therapeutic efficacy. Fifty-one patients with severe recalcitrant AD were treated with interferon gamma (20 patients at low dose and 21 patients at high dose) SQ 3 x weekly for 12 weeks. Both groups reached treatment goals compared to placebo with statistical significance ($p < 0.05$) and the higher dose showed more rapid improvement. The conclusion of the study was that interferon gamma was safe and effective for AD. Since then, there have been 6 other clinical trials, with largest enrolling 51 patients and the longest lasting 24 weeks, all noting improvement. Currently, this indication is considered experimental and investigational due to the lack of larger scale clinical trials or head-to-head clinical trials; coupled with the approval of the

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gold standard biologics such as Dupixent, for treatment of AD which occurred after the 2016 review article was published.

B. Renal Cell Carcinoma

- i. A multicenter, randomized, placebo-controlled, double-blind trial for metastatic renal cell carcinoma was completed in 1999/2000. This trial enrolled 197 patients to receive either placebo or recombinant interferon gamma-1b (60 mcg/m²) SQ every 7 days until disease progression. There was no statistical significance (p=0.75) for the 95% confidence interval of overall response rate of interferon gamma-1b of 4% (1.4-11.5) to placebo of 6% (2.5-13.2). The study concluded with a statement that the lack of efficacy in this trial shows the importance of continued research in this field.

C. Mycosis Fungoides/Sezary Syndrome

- i. Support for this experimental use is supported by the National Comprehensive Cancer Network (NCCN) guidelines for Primary Cutaneous Lymphomas as level of evidence 2a. The trial used in the supporting evidence is from the late 1980s/early 1990s; the phase II trial had a total of 16 patients enrolled with various stages of cutaneous T-cell lymphomas (CTCL). Five patients had partial response with a median response of 10 months, and 6 others showed minor or mixed response. The trial suggested that interferon gamma has efficacy in the treatment of CTCL refractory to use interferon alpha (as being on another interferon was allowed by study design). The quality of this evidence is considered low at this time given the open label trial design, small sample size, and lack of comparator arm.

D. Friederichs's Ataxia

- i. In 2016, Horizon Pharma launched a phase 3 trial, STEADFAST, to evaluate Actimmune for the treatment of Friederichs's Ataxia (FA). The study's primary endpoint was a change from baseline in the modified Friedreich's Ataxia Rating Scale at 26 weeks versus treatment with placebo. The scale is an exam-based rating scale that measuring progression using parameters such as speech, ability to swallow, upper and lower limb coordination, gait, and posture. The trial did not meet statistically significant to this end point or the secondary end points and was stopped prior to original end date due to this finding.

References

1. "Chronic Granulomatous Disease" National Organization for Rare Diseases (NORD) 2018 [Chronic Granulomatous Disease - NORD \(National Organization for Rare Disorders\) \(rarediseases.org\)](https://rarediseases.org)
2. "Osteopetrosis" National Organization for Rare Diseases (NORD) 2018 [Osteopetrosis - NORD \(National Organization for Rare Disorders\) \(rarediseases.org\)](https://rarediseases.org)
3. ACTIMMUNE [Prescribing Information]. Horizon therapeutics Ireland DAC. Dublin Ireland, US License NO 2022
4. Jang I-G, Yang J-K, Lee H-J, et al: Clinical improvement and immunohistochemical findings in severe atopic dermatitis treated with interferon gamma. *J Am Acad Dermatol* 2000; 42:1033-1040.
5. Anjani, Gummadi, Vignesh, Pandiarahan, et al: Recent Advances in chronic granulomatous disease. *Genes & Diseases* Volume 7, Issue 1, March 2020 Pages 84-92 <https://doi.org/10.1016/j.gendis.2019.07.010>
6. Brar K, Leung DY. Recent considerations in the use of recombinant interferon gamma for biological therapy of atopic dermatitis. *Expert Opin Biol Ther.* 2016;16(4):507-514. doi:10.1517/14712598.2016.1135898
7. Elhilali MM, Gleave M, Fradet Y, et al: Placebo-associated remissions in a multicentre, randomized, double-blind trial of interferon gamma-1b for the treatment of metastatic renal cell carcinoma. *BJU International* 2000; 86:613-618.

8. Kaplan EH, Rosen ST, Norris DB, Roenigk HH Jr, Saks SR, Bunn PA Jr. Phase II study of recombinant human interferon gamma for treatment of cutaneous T-cell lymphoma. J Natl Cancer Inst. 1990 Feb 7;82(3):208-12. doi: 10.1093/jnci/82.3.208. PMID: 2104937.
9. "Horizon Pharma plc Announces Topline Results from Phase 3 Study of ACTIMMUNE (interferon gamma-1b) in Friedreich's Ataxia" [Horizon Pharma plc Announces Topline Results from Phase 3 Study of ACTIMMUNE® \(interferon gamma-1b\) in Friedreich's Ataxia | Horizon Therapeutics plc](#) 12/08/2016

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	10/2021

Policy Type: PA

Pharmacy Coverage Policy: UMP040

Description

Ivabradine (Corlanor) is an orally administered direct and selective inhibitor of the hyperpolarization-activated cyclic nucleotide-gated (HCN-gated) channels, or the f-channels that are located in the cardiac sinoatrial node which results in a lowering of the heart rate.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
ivabradine (Corlanor)	5 mg tablets	Heart Failure in Adult Patients;	60 tablets/30 days
	7.5 mg tablets	Heart Failure in Pediatric Patients;	60 tablets/30 days
	5 mg/5 mL solution	Inappropriate Sinus Tachycardia	450 mL/30 days

Initial Evaluation

- I. Ivabradine (Corlanor) may be considered medically necessary when the following criteria below are met:
 - A. Prescribed by or in consultation with a cardiologist; **AND**
 - B. A diagnosis of one of the following:
 1. **Heart Failure in Adult Patients; AND**
 - i. Prescribed by or in consultation with a cardiologist; **AND**
 - ii. The member have stable, symptomatic chronic heart failure; **AND**
 - iii. The member have left ventricular ejection fraction $\leq 35\%$; **AND**
 - iv. The member is in sinus rhythm with resting heart rate ≥ 70 beats per minute; **AND**
 - v. Treatment with maximally tolerated beta-blockers have been ineffective, contraindicated, or not tolerated; **AND**
 - vi. The member does not have any of the following contraindications:
 - a. Acute decompensated heart failure
 - b. Blood pressure less than 90/50 mmHg
 - c. Sick sinus syndrome, sinoatrial block or 3rd degree AV block, unless a functioning demand pacemaker is present
 - d. Resting heart rate less than 60 bpm prior to treatment
 - e. Severe hepatic impairment
 - f. Pacemaker dependence

- g. Concomitant use of strong cytochrome CYP3A4 inhibitors (e.g. azole antifungals, macrolide antibiotics, HIV protease inhibitors);

OR

2. Heart Failure in Pediatric Patients; AND

- i. Member is ≥ 6 months years of age; **AND**
- ii. The member has stable symptomatic heart failure due to dilated cardiomyopathy; **AND**
- iii. The member is in sinus rhythm with elevated heart rate; **AND**
- iv. The member does not have any of the following contraindications:
 - a. Acute decompensated heart failure
 - b. Blood pressure less than 90/50 mmHg
 - c. Sick sinus syndrome, sinoatrial block or 3rd degree AV block, unless a functioning demand pacemaker is present
 - d. Resting heart rate less than 60 bpm prior to treatment
 - e. Severe hepatic impairment
 - f. Pacemaker dependence
 - g. Concomitant use of strong cytochrome CYP3A4 inhibitors (e.g. azole antifungals, macrolide antibiotics, HIV protease inhibitors);

OR

3. Inappropriate Sinus Tachycardia; AND

- i. The member has inappropriate sinus tachycardia; **AND**
- ii. The member does not have any of the following contraindications:
 - a. Acute decompensated heart failure
 - b. Blood pressure less than 90/50 mmHg
 - c. Sick sinus syndrome, sinoatrial block or 3rd degree AV block, unless a functioning demand pacemaker is present
 - d. Resting heart rate less than 60 bpm prior to treatment
 - e. Severe hepatic impairment
 - f. Pacemaker dependence
 - g. Concomitant use of strong cytochrome CYP3A4 inhibitors (e.g. azole antifungals, macrolide antibiotics, HIV protease inhibitors)

II. Ivabradine (Corlanor) is considered not medically necessary when criteria above are not met and/or when used for:

- A. Coronary artery disease with or without heart failure

III. Ivabradine (Corlanor) is considered investigational when used for all other conditions, including but not limited to:

- A. Non-stable, asymptomatic chronic heart failure
- B. Pediatric heart failure not due to dilated cardiomyopathy

Renewal Evaluation

- I. **Heart Failure in adults, heart failure in pediatrics, inappropriate sinus tachycardia; AND**
 - A. Member has previously received treatment with ivabradine (Corlanor); **AND**
 - B. Continues to meet criteria identified in section I of the initial Evaluation; **AND**
 - C. Provider attest to stabilization of disease (e.g. heart rate reduction, reduction in hospitalization due to worsening heart failure); **AND**
 - D. Absence of unacceptable toxicity from the medication

Supporting Evidence

- I. Ivabradine (Corlanor) is indicated to reduce the risk of hospitalization for worsening heart failure in adult patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction $\leq 35\%$, who are in sinus rhythm with resting heart rate ≥ 70 beats per minute and either are on maximally tolerated doses of beta blockers or have a contraindication to beta-blocker use.
- II. ACC/AHA 2015 guideline recommends the use of ivabradine (Corlanor) [moderate evidence] over the historical standard treatment of beta-blockers [weak evidence] for the treatment of inappropriate sinus tachycardia.

Investigational or Not Medically Necessary Uses

- I. Coronary artery disease
 - A. In the BEAUTIFUL and SIGNIFY trials, no benefits were found in patients with stable coronary artery disease with or without stable heart failure, who were given ivabradine (Corlanor).
- II. Non-stable, asymptomatic chronic heart failure
 - A. Ivabradine (Corlanor) has not been studied in patients with non-stable, asymptomatic chronic heart failure; therefore, it would be considered investigational when Corlanor is requested in that setting.
- III. Pediatric heart failure not due to dilated cardiomyopathy
 - A. Ivabradine (Corlanor) has not been studied in pediatric patients with heart failure that is not due to dilated cardiomyopathy; therefore, it would be considered investigational when Corlanor is requested in that setting.

References

1. Corlanor [Prescribing Information]. Thousand Oaks, CA: Amgen, Inc. April 2019.
2. Fox K, Ford I, Steg G, et al. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. [Lancet](#). 2008 Sep 6;372(9641):807-16. doi: 10.1016/S0140-6736(08)61170-8.
3. Ferrari R, Fox K. The role of heart rate may differ according to pathophysiology setting: from SHIFT to SIGNIFY. *Eur Heart J*. 2015;36:2042–2046

Policy Implementation/Update:

Date Created	May 2015
Date Effective	May 2015
Last Updated	August 2015
Last Reviewed	06/2019

Action and Summary of Changes	Date
Transitioned criteria to policy. In this transition, the following updates were made: added new indication for pediatric heart failure due to dilated cardiomyopathy, incorporated the approvable off-label indication of inappropriate sinus tachycardia, and added renewal criteria.	06/2019

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP129

Description

Ixazomib (Ninlaro) is an orally administered reversible proteasome inhibitor that binds and inhibits chymotrypsin-like activity of the beta 5 subunit of the 20s proteasome.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
ixazomib (Ninlaro)	2.3 mg capsule	Previously treated multiple myeloma, in combination with lenalidomide and dexamethasone	3 capsules/28 days
	3 mg capsule		
	4 mg capsule		

Initial Evaluation

- I. Ixazomib (Ninlaro) 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. A diagnosis of **Previously treated multiple myeloma** when the following are met:
 1. The member has relapsed or refractory disease; **AND**
 2. The member has progressed on at least one prior therapy (e.g., melphalan, thalidomide, bortezomib, stem cell transplant, etc.); **AND**
 3. The member has **not** previously progressed on or after lenalidomide (Revlimid); **AND**
 4. Ixazomib (Ninlaro) will be used in combination with lenalidomide (Revlimid) **AND** dexamethasone; **AND**
 5. Ixazomib (Ninlaro) will be **not** be used with any other oncolytic medication other than those noted above.
- II. Ixazomib (Ninlaro) is considered investigational when used for all other conditions, including but not limited to:
 - A. Graft-Versus-Host Disease
 - B. AL Amyloidosis
 - C. Non-Hodgkin lymphoma
 - D. Follicular lymphoma

- E. Breast cancer
- F. Mantle cell lymphoma
- G. Sarcoma
- H. Kidney cancer
- I. Central nervous system cancers

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. Ixazomib (Ninlaro) is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
- IV. Clinical documentation of response to treatment such as stabilization or improvement in disease or symptoms; **AND**
- V. Will be used in combination with lenalidomide (Revlimid) AND dexamethasone; **AND**
- VI. Will **not** be used in combination with any other oncolytic medication other than lenalidomide (Revlimid).

Supporting Evidence

- I. The safety and efficacy of ixazomib (Ninlaro) was evaluated in a randomized, double-blind, placebo controlled trial.
 - Ixazomib (Ninlaro) was evaluated in combination with lenalidomide (Revlimid) and dexamethasone for multiple myeloma in adults. Subjects were relapsed or refractory to at least one prior therapy, with those who were refractory to lenalidomide (Revlimid) excluded from the trial. The label indicates 69% of participants in each group had previously progressed on bortezomib (Velcade), 44-47% had progressed on thalidomide (Thalomid), 80-81% had progressed on melphalan therapy, and 55-59% had previous stem cell transplantation.
 - A total of 722 subjects were randomized and treated until disease progression or unacceptable toxicity with ixazomib (Ninlaro) on days one, eight, and 15 of the 28-day cycles.
 - The primary endpoint was progression-free survival (PFS) according to the 2011 International Myeloma Working Group (IMWG) Consensus Uniform Response Criteria, assessed by a blinded independent review committee. The PFS for ixazomib (Ninlaro) was 20.6 months (17, NE) versus 14.7 months (12.9, 17.6) [HR 0.74 (0.59-0.94), $p < 0.012$].
 - A statistically significant survival benefit has not been demonstrated with ixazomib (Ninlaro).

- II. National Comprehensive Cancer Network guidelines indicate that treatment with a three drug regimen is standard of care; however, for those that have low performance status, initiation with a two-drug regimen may be appropriate until performance improves.
- III. Clinical resources indicate ixazomib (Ninlaro) is approved for multiple myeloma maintenance therapy for newly diagnosed disease; however, the label does not indicate this use. A clinical trial for maintenance therapy after hematopoietic stem cell transplant shows preliminary results for PFS; however, clinically relevant data, such as overall survival, are unknown at this time.

Investigational or Not Medically Necessary Uses

- I. Ixazomib (Ninlaro) has not been sufficiently studied for safety and efficacy, and/or are is currently being evaluated in clinical trials for the following indications:
 - A. Graft-Versus-Host Disease
 - B. AL Amyloidosis
 - C. Non-Hodgkin lymphoma
 - D. Follicular lymphoma
 - E. Breast cancer
 - F. Mantle cell lymphoma
 - G. Sarcoma
 - H. Kidney cancer
 - I. Central nervous system cancers

References

1. Ninlaro [Package Insert]. Cambridge, MA: Millennium Pharmaceuticals, Inc. November 2016.
2. NCCN Clinical Practice Guidelines in Oncology. Multiple Myeloma. Version 2.2019 [Updated October 9, 2019]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf
3. National Institutes of Health. clinicaltrials.gov. Available from www.clinicaltrials.gov. Accessed November 2019.
4. Dimopolulos MA., Gay F., Schjesvold F., et al. Oral ixazomib maintenance following autologous stem cell transplant (TOURMALINE-MM3): a double-blind, randomized, placebo-controlled phase 3 trial. *Lancet*. 2019; 393(10168):253-264.

Policy Implementation/Update:

Date Created	December 2015
Date Effective	February, 2016
Last Updated	November 2019
Last Reviewed	11/2019

Action and Summary of Changes	Date
Prior authorization criteria transitioned to policy format. Age requirement added, as well as clarification on place in therapy and appropriate combination therapy. Renewal requirements changed to include specialist prescriber, and appropriate place in therapy and combination therapy.	11/2019

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP076

Description

Lapatinib (Tykerb) is an orally administered tyrosine kinase inhibitor against epidermal growth factor receptors HER1 and HER2.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
lapatinib (Tykerb)	250 mg tablets	Breast cancer, HER2 overexpression, advanced or metastatic in combination with capecitabine after prior therapy	105 tablets/21 days
		Breast cancer, HR-positive, HER2 overexpression, in postmenopausal women, in combination with letrozole	168 tablets/28 days

Initial Evaluation

- I. **Lapatinib (Tykerb)** may be considered medically necessary when the following criteria below are met:
 - A. The member is 18 years of age or older; **AND**
 - B. Medication is prescribed by, or in consultation with, an oncologist; **AND**
 - C. Lapatinib (Tykerb) will not be used in combination with any other oncolytic medication with the exception of, capecitabine (Xeloda), letrozole, or trastuzumab (Herceptin, Trazimera, Kanjinti, etc.); **AND**
 - D. A diagnosis of **breast cancer** when the following are met:
 1. The tumor is positive for HER2(+) gene expression; **AND**
 2. The breast cancer is advanced (stage III) or metastatic (stage IV); **AND**
 3. The medication will be used in one of the following settings:
 - i. Progression following ALL of the following therapies: anthracycline therapy (e.g., doxorubicin), taxane therapy (e.g., paclitaxel, docetaxel), trastuzumab (e.g., Herceptin, Trazimera, Kanjinti, etc.); **AND**
 - a. Will be used in combination with capecitabine; **AND**
 - b. Request is for generic lapatinib; **OR**
 - i. Member has an intolerance or contraindication to generic lapatinib; **OR**
 - ii. Initial therapy in the metastatic setting; **AND**

- a. The member is a postmenopausal female (natural or pharmacotherapy induced [e.g., GnRH therapy used concomitantly [e.g., Lupron]]); **AND**
 - b. The disease is hormone receptor (HR)-positive; **AND**
 - c. Will be used in combination with letrozole or trastuzumab (Herceptin, Trazimera, Kanjinti, etc.); **AND**
 - d. Request is for generic lapatinib; **OR**
 - i. Member has an intolerance or contraindication to generic labatinib
- II. Lapatinib (Tykerb) is considered investigational when used for all other conditions, including but not limited to:
 - A. HER2(–) breast cancer
 - B. Concurrent use with therapies outside of those listed above
 - C. Ovarian, uterine, endometrial cancer
 - D. Peritoneal cancer
 - E. Pancreatic cancer
 - F. Melanoma
 - G. Central nervous system cancers
 - H. Head and neck cancer
 - I. Gastrointestinal cancer
 - J. Bladder, urothelial, renal cancer

Renewal Evaluation

- I. Member has not been established on therapy by the use of free samples, manufacturer coupons, or otherwise; **AND**
- II. Member has received a previous prior authorization approval for this agent; **AND**
- III. The medication is prescribed by or in consultation with, an oncologist; **AND**
- IV. Lapatinib (Tykerb) will not be used in combination with any other oncolytic medication with the exception of an letrozole, capecitabine or trastuzumab; **AND**
- III. Documentation is provided indicating disease response to therapy, as defined by stabilization of disease, decrease in the size of the tumor, or tumor spread; **AND**
 - A. Request is for generic lapatinib; **OR**
 - 1. Member has an intolerance or contraindication to generic labatinib

Supporting Evidence

- I. Lapatinib (Tykerb) was evaluated in in combination with capecitabine for HER2(+), metastatic breast cancer. The trial was a Phase 3, randomized study versus capecitabine monotherapy in subjects that had previous exposure to anthracyclines, taxanes, and trastuzumab. The primary

endpoint was time to progression and the results were statistically significant in favor of lapatinib (Tykerb).

- II. Overall survival data was not mature at time of assessment, and future results are likely to be confounded as subjects on placebo were allowed to cross over to active therapy during the trial.
- III. In two randomized trials, lapatinib (Tykerb) showed to be less effective than trastuzumab-based chemotherapy regimens. The package label indicates subjects should have disease progression on trastuzumab prior to initiation of lapatinib (Tykerb) when used in combination with capecitabine for those with advanced or metastatic, HER2(+) disease.
- IV. Lapatinib (Tykerb) in combination with letrozole was evaluated in a double-blind, placebo-controlled study. The trial included women with HR+, HER2(+), metastatic breast cancer who had not received prior therapy for metastatic disease. The primary outcome was progression-free survival (PFS) which was statistically significant in favor of lapatinib (Tykerb).
- V. Another trial evaluated lapatinib (Tykerb) in combination with an aromatase inhibitor, again evaluating in HR+, HER2(+), metastatic disease. These subjects had progressed after trastuzumab chemotherapy and endocrine therapies. The treatment arms included lapatinib (Tykerb) + trastuzumab + AI, trastuzumab + AI, or lapatinib (Tykerb) + AI. The results were statistically significant in PFS for the triple therapy, followed by lapatinib (Tykerb) + AI, then trastuzumab + AI. Additionally, lapatinib (Tykerb) has demonstrated a statistically significant improvement in PFS in HER2(+) breast cancer when added to trastuzumab compared to lapatinib (Tykerb) alone.

Investigational or Not Medically Necessary Uses

- I. Lapatinib (Tykerb) has not been sufficiently evaluated for safety and efficacy in the following settings:
 - A. HER2(–) breast cancer
 - B. Concurrent use with therapies outside of those listed above
 - C. Ovarian, uterine, endometrial cancer
 - D. Peritoneal cancer
 - E. Pancreatic cancer
 - F. Melanoma
 - G. Central nervous system cancers
 - H. Head and neck cancer
 - I. Gastrointestinal cancer
 - J. Bladder, urothelial, renal cancer

References

1. Tykerb [Prescribing Information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation. December 2018.
2. Diéras V, Miles D, Verma S, et al. Trastuzumab emtansine versus capecitabine plus lapatinib in patients with previously treated HER2-positive advanced breast cancer (EMILIA): a descriptive analysis of final overall survival results from a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2017;18(6):732-742.
3. Pivot X, Manikhas A, Żurawski B, et al. CEREBEL (EGF111438): A Phase III, Randomized, Open-Label Study of Lapatinib Plus Capecitabine Versus Trastuzumab Plus Capecitabine in Patients With Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer. *J Clin Oncol*. 2015;33(14):1564-73.

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4. Johnston S, Pippen J, Pivot X, et al. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. *J Clin Oncol*. 2009;27(33):5538-46.
5. NCCN Clinical Practice Guideline in Oncology: Breast Cancer. Version 3.2019. National Comprehensive Cancer Network. Available at https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Updated September 6, 2019.
6. Geyer C, Forster J, Lindquist D, et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. *N Engl J Med* 2006;355:2733-2743

Policy Implementation/Update:

Action and Summary of Changes	Date
Added criteria to prefer generic lapatinib over brand Tykerb unless contraindicated or not tolerated	06/2021
Criteria transitioned to policy. Policy updated to include the following requirement: specialist prescriber, age, concurrent therapies, specified place in therapy.	10/2019
Previous Reviews	09/2013
	08/2013
	08/2011
	10/2008
Policy Created	09/2008

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP042

Split Fill Management*

Description

Larotrectinib (Vitrakvi) is an orally administered tropomyosin receptor kinase (TRK) inhibitor; specifically TRKA, TRKB, and TRKC.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
larotrectinib (Vitrakvi)	25 mg capsule	Neutrophic receptor tyrosine kinase gene fusion positive solid tumor, metastatic	180 tablets/30 days
	100 mg capsule		60 tablets/30 days
	20 mg/1 mL solution		Quantity calculated to 100 mg/m ² of body surface area

Initial Evaluation

- I. Larotrectinib (Vitrakvi) may be considered medically necessary when the following criteria are met:
 - A. Prescribed by, or in consultation with, an oncologist; **AND**
 - B. Medication will **not** be used in combination with any other oncolytic medication; **AND**
 - C. The member has **not** previously progressed on other NTRK gene fusion medications (e.g., entrectinib [Rozlytrek]); **AND**
 - D. A diagnosis of solid tumor with confirmed **NTRK gene fusion**; **AND**
 - E. Member has metastatic disease, or surgical resection is likely to result in severe morbidity (i.e., tumor is unresectable); **AND**
 - F. The member does **not** have an acquired resistance mutation (resistant mutations include, but may not be limited to: G595R, G623R, G696A, F617L); **AND**
 - G. **All** alternative therapies for diagnosis and stage of cancer have been exhausted, as defined by:
 1. Progression following all appropriate treatments; **OR**
 2. Nonresponse to all available therapies; **OR**
 3. All available therapies are contraindicated or not tolerated; **OR**
 4. No standard or satisfactory treatments exist; **AND**
 - H. The member has intolerance to or contraindication to entrectinib (Rozlytrek); **OR**

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1. Member is less than 12 years of age
- II. Larotrectinib (Vitrakvi) is considered not medically necessary when criteria above are not met and/or when used for the following:
 - A. When used for a resistance mutation (resistant mutations include, but may not be limited to G595R, G623R, G696A, F617L)
- III. Larotrectinib (Vitrakvi) is considered investigational when used for all other conditions, including but not limited to:
 - A. Oncolytic indications as an adjunct therapy
 - B. Non-small cell lung cancer without NTRK fusion gene rearrangements
 - C. Solid tumors that do not harbor NTRK gene fusions
 - D. Leukemias or lymphomas

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. Prescribed by, or in consultation with, an oncologist; **AND**
- IV. Medication will not be used in combination with any other oncolytic medication; **AND**
- V. Response to therapy as indicated by stabilization of disease or decrease in tumor size or spread; **AND**
- VI. Member does not have unacceptable medication toxicity (e.g., hepatotoxicity, severe delirium or gait disturbances, etc.); **AND**
- VII. Documentation of absence of acquired resistance

Supporting Evidence

- I. Per the landmark trials LOXO-TRK-14001 (SCOUT and NAVIGATE): All subjects were diagnosed with measurable or evaluable metastatic or locally advanced solid tumors, had progressed beyond all effective and available therapies per the National Comprehensive Cancer Network (NCCN), had no therapies available for the diagnosis per NCCN guidelines, or surgical resection would result in significant morbidity.
- II. Subjects were without acquired resistance mutations to NTRK-inhibitors, without active cardiovascular disease or history of myocardial infarction within the prior six months, and were not on concurrent CYP3A4 inhibitors or inducers.
- III. The NTRK gene fusion mutation was confirmed using a validated laboratory testing method. Testing methods for NTRK gene fusion include NGS, RT-PCR, FISH, or Immunohistochemistry (ICH). The use of ICH may lead to a false positive result. ICH uses the presence of a surrogate marker (TRK proteins) to establish the likelihood of a NTRK gene fusion. The FISH method

requires the visual assessment of an experienced pathologist of several tests and is considered more subjective than NGS or RT-PCR.

- IV. The trials were single-arm, open-label studies that included 55 patients with solid tumors. The tumor types that had represented AND reported a measurable Overall Response Rate (ORR) were the following:
- Salivary gland cancer
 - Soft tissue sarcoma (STS)
 - Infantile fibrosarcoma (IFS)
 - Gastrointestinal Stromal Tumor (GIST)
 - Non-small cell lung cancer (NSCLC)
 - Colorectal cancer (CRC)
 - Melanoma
 - Thyroid carcinoma
 - Colon cancer
- V. Tumors that were evaluated in one or more subjects but did not show an ORR included cholangiocarcinoma, appendix, breast and pancreatic cancer.
- VI. Adverse reactions were common with larotrectinib (Vitrakvi), and included fatigue, pyrexia, peripheral edema, CNS, gastrointestinal, respiratory, musculoskeletal, and laboratory disturbances (e.g., ASK, ALT). Adverse events leading to dose discontinuation, interruption or reduction occurred in 37% of subjects. The safety profile of larotrectinib (Vitrakvi) is likely not fully developed given the small number of subjects in the clinical trials and short trial duration. Additionally, due to rarity of the NTRK gene fusion mutation, post-marketing information is likely to remain limited.
- VII. There are currently two available therapies for NTRK gene fusion positive mutations. Larotrectinib (Vitrakvi) and entrectinib (Rozlytrek), currently there is no direct comparison data showing safety and/or efficacy differences between these therapies OR safety or efficacy of using them sequentially after progression. Additionally, caution should be exercised when making cross trial comparisons. At this time, entrectinib (Rozlytrek) provides a better value for general populations with NTRK gene fusion positive tumors given the sum of safety, efficacy, and cost information currently available.
- VIII. It should also be noted that due to single-arm, open-label trial designs, as well as outcomes evaluated, no NTRK gene fusion therapies available have been shown to improve health outcomes to date.
- IX. Entrectinib (Rozlytrek) is FDA-approved down to 12 years of age, but has been, and will continue to be, evaluated in younger populations. Larotrectinib (Vitrakvi) FDA-approval is nonspecific to pediatrics and adults.

Investigational or Not Medically Necessary Uses

- I. Larotrectinib (Vitrakvi) does not have sufficient activity in those with resistance mutations. As of December 2019, known resistance mutations include: G595R, G623R, G696A, F617L.
- II. Larotrectinib (Vitrakvi) has not been sufficiently evaluated for safety and efficacy in the following settings:
 - A. Oncolytic indications as an adjunct therapy

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- B. Non-small cell lung cancer without NTRK fusion gene rearrangements
- C. Solid tumors that do not harbor NTRK gene fusions
- D. Leukemias or lymphomas

** 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. Vitakvi [Prescribing Information]. Stamford, CT: Loxo Oncology, Inc. November 2018.
2. Rozlytrek [Prescribing Information]. Genentech. San Francisco, CA. 2019.
3. Gatalica Z, Swensen J, Kimbrough J, et al. AACR-NCI-EORTC 2017. Abstract A047: Molecular characterization of the malignancies with targetable NTRK gene fusions. Available at: http://mct.aacrjournals.org/content/17/1_Supplement/A047. Accessed December 5, 2018.
4. Hyman DM, Laetsch TW, Kummar S, et al. ASCO 2017. Abstract LBA2501: The efficacy of larotrectinib (LOXO-101), a selective tropomyosin receptor kinase (TRK) inhibitor, in adult and pediatric TRK fusion cancers. Available at: http://ascopubs.org/doi/abs/10.1200/JCO.2017.35.18_suppl.LBA2501. Accessed December 5, 2018.
5. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of Larotrectinib in TRK Fusion-Positive Cancers in Adults and Children. *N Engl J Med*. 2018 Feb 22;378(8):731-739. doi: 10.1056/NEJMoa1714448.
6. Heymach J, Krilov L, Alberg A, et al. Clinical Cancer Advances 2018: Annual Report on Progress Against Cancer From the American Society of Clinical Oncology. *J Clin Oncol*, Vol 36, No 10 (April 1), 2018: pp 1020-1044. DOI: <https://doi.org/10.1200/JCO.2017.77.0446>

Policy Implementation/Update:

Date Created	January 2019
Date Effective	February 2019
Last Updated	December 2019
Last Reviewed	December 2019

Action and Summary of Changes	Date
Policy updated to newest formatting. Initial approval duration changed to three months from six months given safety concerns and split-fill designation, quantity limit for solution now based on BSA, removal of designated test requirement, removed requirements for lab value monitoring, requirement for lack of CV comorbidities and CNS symptoms. Addition of monotherapy requirement, documentation of intolerance of contraindication to entrectinib (Rozlytrek) and requirement the member has not previously progressed on other NTRK therapies.	12/2019

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP310

Description

Lebrikizumab (Ebglyss) is a subcutaneously administered immunoglobulin G4 (IgG4) monoclonal antibody targeting interleukin (IL-13).

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
lebrikizumab (Ebglyss)	Moderate-to-Severe Atopic Dermatitis	250 mg/2 mL syringe/pen	First Month: 4 syringes/pens (8 mL)/28 days Months 2 to 4: 2 syringes/pens (4 mL)/28 days Maintenance: 1 syringe/pen (2 mL)/28 days
		250 mg/2 mL autoinjector	

Initial Evaluation

- I. **Lebrikizumab (Ebglyss)** may be considered medically necessary when the following criteria are met:
 - A. Member is 12 years of age or older; **AND**
 1. If member is under the age of 18 years old, member weighs ≥ 40 kg; **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. Dupilumab, Rinvoq, Otezla, 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 one agent in **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: Branded topical agents (crisaborole [Eucrisa] or ruxolitinib [Opzelura]); **AND**
 3. Treatment with dupilumab (Dupixent) or upadacitinib (Rinvoq) has been ineffective, contraindicated, or not tolerated.

- II. Lebrikizumab (Ebglyss) is considered investigational when used for all other conditions, including but not limited to:
 - A. Use in combination with another biologic or non-biologic specialty therapy (e.g., Dupixent, Rinvoq)
 - B. Pediatric (i.e., age less than 12 years old) atopic dermatitis
 - C. Asthma
 - D. 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. 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. Dupilumab, Rinvoq, Otezla, 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, crisaborole (Eucrisa) [a PDE4 inhibitor], and/or ruxolitinib (Opzelura) [a topical JAK 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 the 2014 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), dupilumab (Dupixent), tralokinumab (Adbry), upadacitinib (Rinvoq), and abrocitinib (Cibinqo). Dupilumab (Dupixent) and tralokinumab (Adbry) are biologic options while upadacitinib (Rinvoq) and abrocitinib (Cibinqo) are oral JAK inhibitors for moderate-to-severe AD. Currently, there are no head-to-head trials evaluating safety and/or efficacy differences or superiority between lebrikizumab (Ebglyss) and other therapies. Dupilumab (Dupixent) has an established safety and efficacy profile for the treatment of atopic dermatitis and is approved down to six months of age. Upadacitinib (Rinvoq), and abrocitinib (Cibinqo) are

FDA-approved for use in adolescents and adults in the same setting as lebrikizumab (Ebglyss). Tralokinumab (Adbry) is reserved for use in adults aged 18 years and older only.

- 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 National Institute for Health and Care Excellence (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. Lebrikizumab (Ebglyss) was evaluated in three randomized, double-blind, placebo-controlled, Phase III clinical trials, two trials as monotherapy (ADVOCATE1 and ADVOCATE2) and one in addition to topical corticosteroids (ADHERE). Patients were randomized 2:1 to receive lebrikizumab (Ebglyss), administered as a 500mg loading dose on days 0 and 14, followed by 250mg every two weeks, or placebo. Patients enrolled in the clinical trials were 12 years of age and older (weighing $\geq$ 40 kg), had a diagnosis of moderate-to-severe atopic dermatitis (IGA 3 or 4) with BSA of at least 10% who had insufficient response to topical therapies and were candidates for systemic therapy. Previous use of systemic treatment was recorded for approximately 55% of the patients enrolled in the clinical trials.
- VI. The primary efficacy outcome for all three trials was the percentage of patients with an IGA score of 0 (clear) or 1 (almost clear) and a $\geq$ 2 point improvement from baseline at week 16. Key secondary endpoints included EASI-75 and EASI-90 at week 16, and reduction in Pruritis NRS score of $\geq$ 4 points at week 4. All notable endpoints were met in the clinical trials, as noted in the table below.

	ADHERE		ADVOCATE1		ADVOCATE2	
	Lebrikizumab (N=145)	Placebo (N=66)	Lebrikizumab (N=283)	Placebo (N=141)	Lebrikizumab (N=281)	Placebo (N=146)
IGA 0 or 1	41.2%	22.1%	43.1%	12.7%	33.2%	10.8%
	P=0.01		P<0.001		P<0.001	
EASI-75	69.5%	42.2%	58.8%	16.2%	52.1%	18.1%
	P<0.001		P<0.001		P<0.001	
EASI-90	41.2%	21.7%	38.8%	9.0%	30.7%	9.5%
	P=0.008		P<0.001		P<0.001	
Reduction in Pruritis NRS $\geq$ 4 points	50.6%	31.9%	21.5%	2.3%	16.8%	3.0%
	P<0.05		P<0.001		P<0.001	

- VII. In the ADVOCATE 1 and 2 trials, responders to therapy at week 16 were re-randomized to receive lebrikizumab (Ebglyss) 250mg every 2 weeks or every 4 weeks during the maintenance phase through week 52. The efficacy results from the induction phase of the ADVOCATE 1 and 2 were maintained through the maintenance phase, with nearly half of the patients obtaining IGA 0 or 1 (with $\geq$ 2 point improvement) and approximately 67% achieving EASI-75 and Pruritis NRS $\geq$ 4-point improvement from baseline.

- VIII. The safety profile of lebrikizumab (Ebglyss) is similar to other monoclonal antibodies FDA-approved for atopic dermatitis. The majority of treatment emergent adverse events (TEAEs) reported during the clinical trials were mild or moderate in severity, with the most common TEAEs including conjunctivitis (6.6% vs. 1.6% placebo), headache (4.3% vs. 2.3% placebo), and nasopharyngitis (3.7% vs. 3.7% placebo). Potential opportunistic infections were reported in 2.1% of lebrikizumab (Ebglyss) treated patients in the ADHERE trial, while none were reported in either ADVOCATE trials.
- IX. 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 formulary therapies should be utilized first based on cost-effectiveness.

Investigational or Not Medically Necessary Uses

- I. Lebrikizumab (Ebglyss) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
- A. Use in combination with another biologic or non-biologic specialty therapy (e.g., Dupixent, Rinvoq)
 - B. Pediatric (i.e., age less than 12 years old) atopic dermatitis
 - C. Asthma
 - D. Psoriasis

References

- Silverberg JI, Guttman-Yassky E, Thaçi D, et al. Two Phase 3 Trials of Lebrikizumab for Moderate-to-Severe Atopic Dermatitis. *N Engl J Med*. 2023;388(12):1080-1091. doi:10.1056/NEJMoa2206714
- Blauvelt A, Thyssen JP, Guttman-Yassky E, et al. Efficacy and safety of lebrikizumab in moderate-to-severe atopic dermatitis: 52-week results of two randomized double-blinded placebo-controlled phase III trials. *Br J Dermatol*. 2023;188(6):740-748. doi:10.1093/bjd/ljad022
- Simpson EL, Gooderham M, Wollenberg A, et al. Efficacy and Safety of Lebrikizumab in Combination With Topical Corticosteroids in Adolescents and Adults With Moderate-to-Severe Atopic Dermatitis: A Randomized Clinical Trial (ADhere) [published correction appears in *JAMA Dermatol*. 2023 Jul 19;:]. *JAMA Dermatol*. 2023;159(2):182-191. doi:10.1001/jamadermatol.2022.5534
- Lebrikizumab pre-launch product dossier. Eli Lilly. April 12, 2023.
- American Academy of Dermatology. Guidelines of care for the management of atopic dermatitis – Section 2: Management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol* 2014;71:116-32.
- American Academy of Dermatology. Guidelines of care for the management of atopic dermatitis – Section 3: Management and treatment of atopic dermatitis with phototherapy and systemic agents. *J Am Acad Dermatol* 2014;71:132-49.

Related Policies

Policy Name	Disease state
Chronic Inflammatory Disease Policy and Systemic Janus Associated Kinase (JAK) Inhibitors in Chronic Inflammatory Disease Policy	Rheumatoid Arthritis
	Polyarticular Juvenile Idiopathic Arthritis (PJIA)
	Systemic Juvenile Idiopathic Arthritis (SJIA)
	Psoriatic Arthritis
	Ankylosing Spondylitis
	Non-radiographic Axial Spondyloarthritis
	Plaque Psoriasis

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	Crohn's Disease
	Ulcerative Colitis
	Behcet's Disease (i.e., Behcet Syndrome)
	Hidradenitis Suppurativa
	Uveitis and Panuveitis
	Giant Cell Arteritis
	Cryopyrin-Associated Periodic Syndromes (CAPS)
	Recurrent Pericarditis
	Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD)
	Atopic Dermatitis
Ruxolitinib (Jakafi®, Opzelura™) Policy	Intermediate or high-risk myelofibrosis
	Polycythemia vera
	Graft-Versus-Host Disease
	Atopic dermatitis
Dupilumab (Dupixent®) Policy	Atopic Dermatitis
	Asthma (moderate to severe)
	Chronic rhinosinusitis with nasal polyposis
	Eosinophilic esophagitis
Tralokinumab (Adbry™) Policy	Prurigo nodularis
	Atopic Dermatitis

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated QLL to align with FDA label; Updated criteria to reflect plan's preferred agents	09/2024
Policy created	11/2023

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP111

Description

Thalidomide (Thalomid) is an oral immunomodulatory medication that inhibits FGF-dependent angiogenesis in vivo and exhibits antineoplastic activity. Lenalidomide (Revlimid) and pomalidomide (Pomalyst) are orally administered thalidomide analogues. These agents are thought to attack multiple targets in the microenvironment of the myeloma cell, producing apoptosis, inhibition of angiogenesis, and cytokine circuits, among others.

Length of Authorization

- **Initial:**
 - i. Lenalidomide (Revlimid)
 1. Follicular lymphoma/Marginal zone lymphoma: 12 months
 2. All other indications: Six months
 - ii. Pomalidomide (Pomalyst) and thalidomide (Thalomid)
 1. All indications: Three months
- **Renewal:**
 - i. Lenalidomide (Revlimid)
 1. Follicular lymphoma/Marginal zone lymphoma: Cannot be renewed
 2. All other indications: 12 months
 - ii. Pomalidomide (Pomalyst)
 1. All indications: 12 months
 - iii. Thalidomide (Thalomid)
 1. Cutaneous manifestations of moderate to severe Erythema Nodosum Leprosum (ENL): 12 months
 2. Multiple myeloma: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
generic lenalidomide	2.5 mg capsules	Follicular lymphoma; Marginal zone lymphoma; Multiple myeloma; Myelodysplastic syndromes	28 capsules/28 days
	5 mg capsules	Follicular lymphoma; Mantle cell lymphoma; Marginal zone lymphoma; Multiple myeloma; Multiple myeloma maintenance therapy following auto-HSCT; Myelodysplastic syndromes;	28 capsules/28 days
	10 mg capsules		28 capsules/28 days
	15 mg capsules		28 capsules/28 days
	20 mg capsules	Mantle cell lymphoma; Multiple myeloma	21 capsules/28 days
	25 mg capsules		21 capsules/28 days

lenalidomide (Revlimid)	2.5 mg capsules	Follicular lymphoma; Marginal zone lymphoma; Multiple myeloma; Myelodysplastic syndromes	28 capsules/28 days
	5 mg capsules	Follicular lymphoma; Mantle cell lymphoma; Marginal zone lymphoma; Multiple myeloma; Multiple myeloma maintenance therapy following auto-HSCT; Myelodysplastic syndromes;	28 capsules/28 days
	10 mg capsules		28 capsules/28 days
	15 mg capsules		28 capsules/28 days
	20 mg capsules		21 capsules/28 days
	25 mg capsules	Mantle cell lymphoma; Multiple myeloma	21 capsules/28 days
pomalidomide (Pomalyst)	1 mg capsules	Multiple Myeloma	21 capsules/28 days
	2 mg capsules		
	3 mg capsules		
	4 mg capsules		
thalidomide (Thalomid)	50 mg capsules	Multiple Myeloma	28 capsules/28 days
	100 mg capsules		
	150 mg capsules		
	200 mg capsules		
	50 mg capsules	Erythema Nodosum Leprosum	60 capsules/30 days
	100 mg capsules		
	150 mg capsules		
	200 mg capsules		

Initial Evaluation

- I. **Lenalidomide (Revlimid) and generic lenalidomide** may be considered medically necessary when the following criteria are met:
 - A. Medication is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
 - B. Request is for generic lenalidomide; **OR**
 1. Request is for BRAND Revlimid and treatment with generic lenalidomide is contraindicated or not tolerated; **AND**
 - C. A diagnosis of **multiple myeloma (MM)** when the following is met:
 1. Medication will be used with dexamethasone as part of a doublet or triplet regimen; **OR**
 2. Medication will be used as monotherapy; **OR**
 - D. A diagnosis of **myelodysplastic syndrome (MDS)** when the following are met:
 1. Member has lower risk disease (e.g. IPSS Low or Intermediate-1; IPSS-R Very Low, Low, Intermediate; WPSS Very Low, Low, Intermediate); **AND**
 2. Member has transfusion-dependent anemia (i.e. 2 or more units of red blood cells in the previous 8 weeks); **AND**
 - i. MDS with del(5q) abnormality; **OR**

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- ii. MDS without del(5q) abnormality; **AND**
 - a. Serum erythropoietin levels are less than 500 mU/mL; **AND**
 - i. Medication will be used in combination with an erythropoiesis-stimulating agent (ESA) (e.g. Procrit, Retacrit, or Aranesp) with or without granulocyte-colony stimulating factor (GCSF) (e.g., filgrastim, pegfilgrastim); **AND**
 - 1. History of inadequate response to ESA with or without GCSF; **OR**
 - b. Serum erythropoietin levels are greater than 500 mU/mL; **AND**
 - i. History of failure, contraindication, or intolerance to immunosuppressive therapy (IST) (e.g. anti-thymocyte globulin ± cyclosporine A); **OR**
 - E. A diagnosis of **mantle cell lymphoma (MCL)** when the following is met:
 - 1. Member has relapsed or progressed after two prior regimens, one of which included bortezomib; **OR**
 - F. A diagnosis of **follicular lymphoma (FL)** when the following are met:
 - 1. Member was previously treated with at least one prior regimen for FL (e.g. bendamustine + rituximab/obinutuzumab, cyclophosphamide/doxorubicin/vincristine/prednisone); **AND**
 - 2. The medication will be used in combination with rituximab; **OR**
 - G. A diagnosis of **marginal zone lymphoma (MZL)** when the following are met:
 - 1. Member was previously treated with at least one prior regimen for MZL (e.g. bendamustine + rituximab, rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone, rituximab/cyclophosphamide/vincristine/prednisone); **AND**
 - 2. The medication will be used in combination with rituximab
- II. **Pomalidomide (Pomalyst)** may be considered medically necessary when the following criteria are met:
- A. Medication is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
 - B. A diagnosis of **multiple myeloma (MM)** when the following are met:
 - 1. Member has relapsed and/or refractory MM; **AND**
 - 2. Member has received at least two prior therapies for MM, including lenalidomide (Revlimid) and a proteasome inhibitor (e.g. bortezomib); **AND**
 - 3. Medication will be initiated within 60 days of completion of the last therapy; **AND**
 - 4. Medication will be used with dexamethasone as part of a doublet or triplet regimen
- III. **Thalidomide (Thalomid)** may be considered medically necessary when the following criteria are met:
- A. Medication is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
 - 1. A diagnosis of **multiple myeloma (MM)** when the following are met:

- i. Medication will be used with dexamethasone as part of a doublet or triplet regimen; **OR**
 - B. Medication is prescribed by, or in consultation with, an infectious disease specialist
 - 1. A diagnosis of **erythema nodosum leprosum (ENL)** when the following are met:
 - i. Medication will be used for the acute treatment of the cutaneous manifestations of moderate to severe ENL; **AND**
 - a. If moderate to severe neuritis is present, the medication will be used in combination with corticosteroids; **OR**
 - ii. Medication will be used as maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrence
- IV. Lenalidomide (Revlimid) is considered not medically necessary when used for all other conditions, including but not limited to:
 - A. Chronic lymphocytic leukemia (CLL), relapsed or refractory
- V. Lenalidomide (Revlimid), pomalidomide (Pomalyst), and thalidomide (Thalomid) is/are considered investigational when used for all other conditions, including but not limited to:
 - A. Kaposi sarcoma)
 - B. Behçet syndrome
 - C. Diffuse large B-cell lymphoma (DLBCL)
 - D. Multiple myeloma (MM) when given as part of a quadruplet (“quad”) regimen
 - E. Myelofibrosis
 - F. Non-Hodgkin's lymphoma (NHL)
 - G. POEMS syndrome
 - H. Systemic light chain amyloidosis (AL)

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 response to treatment defined by improvement or stabilization of disease or symptoms; **AND**
- IV. Request is for pomalidomide (Pomalyst), thalidomide (Thalomid), or generic lenalidomide; **OR**
 - A. Request is for BRAND Revlimid and treatment with generic lenalidomide has been ineffective, contraindicated, or not tolerated

Supporting Evidence

- I. **Multiple myeloma (MM):**
 Lenalidomide (Revlimid)

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- Efficacy of lenalidomide (Revlimid) was established in an open-label trial comparing lenalidomide (Revlimid) with low dose dexamethasone (Rd) to melphalan, prednisone, and thalidomide (Thalomid) (MPT) in newly diagnosed MM patients who were not candidates for stem cell transplant. The primary outcome of progression free survival (PFS) was significantly longer with Rd continuous than MPT: HR 0.72 (95% CI: 0.61-0.85 p <0.0001). The improvement in median PFS time in the Rd continuous arm compared with the MPT arm was 4.3 months.
- In MM patients following auto-HSCT, efficacy was established in two multicenter, randomized, double-blind, parallel group, placebo-controlled studies. In both studies, the primary analysis of PFS was significantly longer with lenalidomide (Revlimid) compared to placebo.
- Numerous regimens have been used for the treatment of MM, both in patients who are transplant eligible and those who are not transplant eligible.
- Three-drug regimens are the mainstay of initial therapy for most patients with newly diagnosed MM. For all patients with MM, regardless of transplant status, triplet regimens have shown to induce higher response rates and depth of response in clinical trials.
 - i. Lenalidomide (Revlimid)/bortezomib/dexamethasone
 - 1. Phase 2 and Phase 3 trials have demonstrated that initial treatment with the combination is active and well tolerated in newly diagnosed patients with MM, regardless of transplant eligibility.
 - 2. This combination is included as a preferred NCCN category 1 recommendation for primary therapy for both MM patients, regardless of transplant status.
 - ii. Lenalidomide (Revlimid)/low-dose dexamethasone
 - 1. Two-drug regimens are typically reserved for elderly and/or frail patients.
 - 2. Lenalidomide (Revlimid) in combination with low-dose dexamethasone is a well-tolerated and effective regimen for transplant-ineligible and elderly patients.
 - 3. This combination is included as a preferred NCCN category 1 recommendation for primary therapy for non-transplant candidates.
 - iii. Lenalidomide (Revlimid)/daratumumab (Darzalex)/dexamethasone
 - 1. An open-label, randomized, active control Phase 3 study compared treatment with the addition of daratumumab (Darzalex) to lenalidomide (Revlimid)/dexamethasone compared to lenalidomide (Revlimid)/dexamethasone alone in 737 patients with newly diagnosed MM ineligible for transplant.
 - 2. Median PFS has not been reached in the triplet combination arm compared to 31.9 months in the control arm.
 - 3. This combination is included as a preferred NCCN category 1 recommendation for primary therapy for non-transplant candidates.

- Lenalidomide (Revlimid) is also used in previously treated MM, typically as part of similar triplet regimens.
 - i. Lenalidomide (Revlimid)/bortezomib/dexamethasone
 1. The results of Phase 1 and Phase 2 studies show that the triplet combination is well tolerated and active, with durable responses in heavily pretreated patients with relapsed and/or refractory MM, including patients who have had prior lenalidomide (Revlimid), bortezomib, thalidomide, and transplant.
 2. After a median follow-up of 44 months, the median PFS was 9.5 months and median overall survival (OS) was 30 months.
 3. This combination is included as a preferred NCCN category 2A recommendation for previously treated MM
 - ii. Lenalidomide (Revlimid)/elotuzumab (Empliciti)/dexamethasone
 1. This combination is FDA approved for the treatment of patients with MM who have received one to three prior therapies.
 2. Efficacy and safety were demonstrated in a Phase 3 trial which randomized 646 patients to receive either elotuzumab (Empliciti) in combination with lenalidomide (Revlimid) and dexamethasone or lenalidomide (Revlimid)/dexamethasone alone.
 3. Median PFS in the elotuzumab (Empliciti)-containing regimen was 19.4 months vs 14.9 months in those receiving lenalidomide (Revlimid)/dexamethasone alone.
 4. This combination is included as a preferred NCCN category 1 recommendation for previously treated MM.
 - iii. Lenalidomide (Revlimid)/carfilzomib (Kymriah)/dexamethasone
 1. The combination was evaluated in a randomized, open-label trial compared to lenalidomide (Revlimid)/dexamethasone alone in patients with relapsed and/or refractory MM.
 2. Median PFS was 26.3 months for the triple combination therapy vs 17.6 months for lenalidomide (Revlimid)/dexamethasone.
 3. This combination is included as a preferred NCCN category 1 recommendation for previously treated MM.
 - iv. Lenalidomide (Revlimid)/daratumumab (Darzalex)/dexamethasone
 1. A Phase 3 trial in 569 patients evaluated the addition of daratumumab (Darzalex) to lenalidomide (Revlimid)/dexamethasone vs lenalidomide (Revlimid)/dexamethasone alone.
 2. The overall response rate (ORR) was higher in the daratumumab group, and the estimated rate of PFS at 12 months was 83.2% compared with 60% in the control group.
 3. This combination is included as a preferred NCCN category 1 recommendation for previously treated MM.
 - v. Lenalidomide (Revlimid)/ixazomib (Ninlaro)/dexamethasone

1. The combination is FDA approved for the treatment of patients with MM who have received at least one prior therapy.
2. The safety and efficacy were evaluated in a randomized, controlled trial in patients who had received at least one prior MM therapy (e.g. bortezomib-containing regimen). Patients were randomized to lenalidomide (Revlimid)/ixazomib (Ninlaro)/dexamethasone vs lenalidomide (Revlimid)/dexamethasone alone.
3. The triple combination resulted in a PFS of 20.6 months compared to 14.7 months for the control arm.
4. This combination is included as a preferred NCCN category 1 recommendation for previously treated MM.

Pomalidomide (Pomalyst)

- Pomalidomide (Pomalyst) is indicated for patients with multiple myeloma, in combination with dexamethasone, who have received at least two prior therapies including lenalidomide (Revlimid) and a proteasome inhibitor and have demonstrated disease progression on or within 60 days of last therapy.
- A Phase 3 randomized, open-label study compared the efficacy and safety of pomalidomide (Pomalyst) and low-dose dexamethasone vs high-dose dexamethasone in patients with relapsed MM who were refractory to both lenalidomide (Revlimid) and bortezomib. The primary endpoint, PFS, was significantly longer in patients who received pomalidomide (Pomalyst) and low-dose dexamethasone compared to those who received high-dose dexamethasone (4.0 vs 1.9 months; $P < 0.0001$). Overall survival was significantly longer in the pomalidomide (Pomalyst) group also (12.7 vs 8.1 months; $P = 0.0285$).
- A Phase 2, randomized open-label trial evaluated the safety and efficacy of pomalidomide (Pomalyst) alone or pomalidomide (Pomalyst) with low-dose dexamethasone in patients with relapsed or refractory MM. The ORR was 29.2% in patients who received combination therapy versus 7.4% in the monotherapy arm.
- Additional data regarding single agent pomalidomide (Pomalyst) therapy is available but is considered low quality. Pomalidomide (Pomalyst) monotherapy was evaluated in a Phase 1 trial of 24 patients and demonstrated an ORR of 50%. In a subsequent Phase 1 study, the ORR was much lower at 15%.
- Immunomodulatory agents are usually given in combination with dexamethasone and/or other agents, but the NCCN Multiple Myeloma Panel suggests considering pomalidomide (Pomalyst) monotherapy in patients who are steroid-intolerant.

Thalidomide (Thalomid)

- Although thalidomide (Thalomid) was the first immunomodulatory agent to show efficacy in MM, other agents such as lenalidomide (Revlimid) and pomalidomide (Pomalyst) have since been developed and offer a more favorable safety profile.
- The efficacy and safety of thalidomide (Thalomid) plus dexamethasone vs dexamethasone alone in multiple myeloma was evaluated in two open-label studies in symptomatic patients with newly diagnosed multiple myeloma. In one study, response rates (based on serum or urine paraprotein measurements) were

significantly higher in the combination arm (52% vs 36%). In another study, the time to progression (TTP) was statistically significantly longer in the combination arm.

- The NCCN Guideline for Multiple Myeloma does not include thalidomide (Thalomid)-based regimens as preferred or recommended for any setting. Regimens containing thalidomide (Thalomid) may be useful in certain circumstances when used in combination with other active multiple myeloma agents (e.g. bortezomib). The combination of bortezomib, thalidomide (Thalomid), and dexamethasone is a Category 1 recommendation as primary therapy for transplant candidates in certain circumstances.
- There is no evidence to support the use of thalidomide (Thalomid) as monotherapy for the treatment of multiple myeloma.

II. **Myelodysplastic syndromes (MDS):**

- Lower-risk MDS with del(5q) generally has a relatively good prognosis and is highly responsive to lenalidomide (Revlimid) therapy.
 - i. A Phase 3 trial in 205 patients demonstrated superiority of lenalidomide (Revlimid) compared to placebo for achieving RBC transfusion-independence.
 1. Patients with transfusion-dependent, lower risk MDS with del(5q) were treated with low dose lenalidomide (Revlimid) (10 mg), lower dose lenalidomide (Revlimid) (5 mg), and placebo.
 2. The rates of transfusion-independence for greater than 26 weeks were 57%, 37%, and 2% respectively for low dose lenalidomide (Revlimid), lower dose lenalidomide (Revlimid), and placebo.
 3. The risk of transformation to acute myeloid leukemia (AML) was not significantly different between lenalidomide (Revlimid) and placebo.
 - ii. Additionally, a Phase 2 trial in anemic transfusion-dependent patients with del(5q) also reported similar hematologic responses in two-thirds of the 148 patients with del(5q).
- The safety and efficacy of lenalidomide (Revlimid) for lower-risk MDS without del(5q) was evaluated in a Phase 3 trial in 239 patients with transfusion-dependent MDS.
 - i. Patients receiving lenalidomide (Revlimid) compared to placebo had a higher rate of transfusion-independence (26.9% vs 2.5%; $p < 0.001$). Transfusion reduction of four or more units of packed RBCs was seen in 22% of lenalidomide (Revlimid)-treated patients while no reduction was seen in the placebo group.
 - ii. Incidence of treatment-related mortality was 2.5% in both groups, but the incidence of myelosuppression was higher in the lenalidomide-treated group. Furthermore, when comparing lenalidomide (Revlimid) to placebo, the incidence of grade 3 or 4 neutropenia was 61.9% vs 12.7%, respectively, and the rate of thrombocytopenia was 35.6% vs 3.8%, respectively.

III. **Mantle cell lymphoma (MCL):**

- Lenalidomide (Revlimid) is approved for the treatment of patients with MCL whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib.
- The safety and efficacy of single-agent lenalidomide (Revlimid) for relapsed or refractory MCL was evaluated in a Phase 2, open-label trial in 134 patients with prior bortezomib therapy. The ORR was 28% and a median duration of response (DoR) was 16.6 months.
- An additional Phase 2 trial included 254 patients with relapsed MCL who were not candidates for intensive therapy were randomized to receive single-agent lenalidomide (Revlimid) or single-agent of the investigator's choice (e.g. rituximab, gemcitabine, fludarabine, chlorambucil, cytarabine) and were allowed to receive lenalidomide (Revlimid) at the time of progression. After a median follow-up of 15.9 months, PFS was 8.7 months for lenalidomide (Revlimid) versus 5.2 months for the control arm.
- The NCCN B-Cell Lymphomas guideline suggests the use of lenalidomide (Revlimid) outside of the relapsed/refractory setting, including as initial treatment or in the second-line setting. However, there is limited evidence to support use outside of the relapsed/refractory setting. A small Phase 2 study evaluated the use of lenalidomide (Revlimid) plus rituximab as initial therapy for patients with MCL. The ORR in the intention-to-treat population (n = 38) was 87% and 92% in the population that could be evaluated (n = 36).

IV. Previously treated follicular lymphoma (FL)/marginal zone lymphoma (MZL):

- The efficacy of lenalidomide (Revlimid) with rituximab in patients with relapsed or refractory follicular and marginal zone lymphoma was evaluated in the AUGMENT (NCT01938001) and MAGNIFY (NCT01996865) trials.
- AUGMENT was a randomized, double-blind, multicenter trial (n=358) in patients with relapsed or refractory follicular or marginal zone lymphoma who received lenalidomide (Revlimid) and rituximab or rituximab and placebo for a maximum of 12 cycles or until unacceptable toxicity.
 - i. Efficacy results in the follicular and marginal zone lymphoma population reported a PFS of 39.4 months in the lenalidomide (Revlimid) and rituximab arm versus 14.1 months in the rituximab plus placebo arm.
- MAGNIFY is an open-label, multicenter trial (n=232) in which patients with relapsed or refractory follicular, marginal zone, or mantle cell lymphoma received 12 induction cycles of lenalidomide (Revlimid) and rituximab.
 - i. Overall response by investigator assessment was 59% (104/177) [95% CI: 51, 66] for patients with follicular lymphoma. Median DoR was not reached within a median follow-up time of 7.9 months [95% CI: 4.6, 9.2]. With an overall response of 51% (23/45) [95% CI: 36, 66] for patients with marginal zone lymphoma and median DoR not reached within a median follow-up time of 11.5 months [95% CI: 8.0, 18.9].

V. Erythema nodosum leprosum (ENL)

- Erythema nodosum leprosum (ENL) is a serious immunological complication of leprosy, causing inflammation of skin, nerves, other organs, and general malaise.

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There is limited high-quality, prospective data supporting the use of thalidomide (Thalomid) for ENL. Data are mainly derived from small randomized trials or retrospective studies conducted by the U.S. Public Health Service. These data consistently report generally successful treatment of the cutaneous manifestations of moderate to severe ENL.

- Thalidomide (Thalomid) is not indicated as monotherapy for ENL treatment in the presence of moderate to severe neuritis. Patients who have a documented history of requiring prolonged maintenance treatment to prevent the recurrence of cutaneous ENL or who flare during tapering should be maintained on the minimum dose necessary to control the reaction. Tapering off the medication should be attempted every 3 to 6 months, in decrements of 50 mg every 2 to 4 weeks.
- Dosing with thalidomide (Thalomid) in ENL should usually continue until signs and symptoms of active reaction have subsided, usually a period of at least 2 weeks. Patients may then be tapered off medication in 50 mg decrements every 2 to 4 weeks.
- In patients with moderate to severe neuritis associated with a severe erythema nodosum leprosum reaction, corticosteroids may be started concomitantly with thalidomide (Thalomid). Steroid usage can be tapered and discontinued when the neuritis has improved.

Investigational or Not Medically Necessary Uses

I. Kaposi sarcoma

- A preliminary study of thalidomide (Thalomid) has shown some activity in patients with AIDS-related KS; however, further evaluation is needed to support use of lenalidomide (Revlimid) in this setting.
- Pomalidomide (Pomalyst) was studied in one ongoing, open-label, single center, single arm, Phase 1/2 trial with 28 patients with KS. There were 18 HIV-positive patients and 10 HIV-negative patients included in the trial. The HIV-positive patients continued on HAART. The primary efficacy outcome was ORR. The ORR was 71% (95% CI 51, 87) for all patients with 12 HIV-positive patients and 8 HIV-negative patients having a response. The duration of response was 12.5 months (95% CI 6.5, 24.9) for HIV-positive patients and 10.5 months (95% CI 3.9, 24.2) for HIV-negative patients. NCCN guidelines recommend pomalidomide (Pomalyst) as the preferred subsequent systemic therapy for relapsed/refractory therapy after first-line systemic options liposomal doxorubicin or paclitaxel; however, this is based on preliminary evidence from an early-phase, single center, open-label trial. Further evaluation in larger, well-controlled studies are needed to support the use of pomalidomide (Pomalyst) in the setting of KS.

II. Behçet syndrome

- The efficacy of thalidomide monotherapy for mucocutaneous manifestations of Behçet syndrome was evaluated in 96 patients compared to placebo. Only a minority of thalidomide (Thalomid)-treated patients responded to treatment, and some symptoms worsened. Furthermore, 7% of thalidomide-treated patients developed peripheral neuropathy.

- B. The use of thalidomide (Thalomid) for Behçet syndrome has fallen out of favor due to lack of proven efficacy and significant risk of neuropathy and teratogenicity.
- III. Chronic lymphocytic leukemia (CLL)
 - A. Lenalidomide (Revlimid) was studied in patients with previously treated CLL in a randomized, double-blind, placebo-controlled, Phase 3 trial (CONTINUUM). Patients included in the trial had been treated with two lines of therapy with at least a partial response after second-line therapy, had received a purine analogue, bendamustine, anti-CD20 antibody, chlorambucil, or alemtuzumab as first-line or second-line treatment; and had an Eastern Cooperative Oncology Group performance score of 0–2. Co-primary endpoints were PFS and OS; the primary endpoint was later changed to OS after the data cutoff for analysis. With a median follow-up of 31.5 months, there was no significant difference in OS between the lenalidomide (Revlimid) and the placebo groups (median 70.4 months, 95% CI 57.5–not estimable [NE] vs NE, 95% CI 62.8–NE; hazard ratio [HR] 0.96, 95% CI 0.63–1.48; $p=0.86$).
- IV. Diffuse large B-cell lymphoma (DLBCL)
 - A. NCCN guidelines list lenalidomide (Revlimid) maintenance for patients 60–80 years of age as a Category 2B recommendation. This is based off the results of an open-label, single-arm, Phase 2 trial in 48 adults with de novo DLBCL. Further evaluation in higher quality trials is needed to support its use.
 - B. In the relapsed setting, lenalidomide (Revlimid) was studied in small, Phase 2, open-label trials consisting of low-quality evidence. Further evaluation is needed to support use of lenalidomide (Revlimid) in this setting.
- V. Multiple myeloma, as part of quadruple (“quad”) regimen
 - A. Although triplet regimens remain the standard of care for MM, 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.
- VI. Non-Hodgkin's lymphoma (NHL)
 - A. Lenalidomide (Revlimid) was evaluated in patients with relapsed or refractory aggressive NHL, in an open-label, Phase 2 trial ($n=49$). Treatment with lenalidomide (Revlimid) led to an ORR of 35% and a median PFS of 4 months. Further evaluation is needed to support use of lenalidomide (Revlimid) in this setting.
- VII. Myelofibrosis
 - A. Lenalidomide (Revlimid) was evaluated in a small, open-label, Phase 2 trial in combination with prednisone that reported a treatment response in 10 of 42 subjects, with 37 patients reporting a grade 3 or 4 toxicity. In an analysis of three consecutive Phase 2 trials of patients with myelofibrosis ($n=125$), single agent lenalidomide (Revlimid) and lenalidomide (Revlimid) plus prednisone produced higher response rates than thalidomide (Thalomid), though not statistically significant ($p=0.06$). Further studies are warranted. An additional trial by Daver et al. that evaluated lenalidomide (Revlimid) in combination with ruxolitinib (Jakafi) was terminated early due to failure to meet the predetermined efficacy rules for treatment success.

- B. Pomalidomide (Pomalyst) has been evaluated as a treatment option for MF-associated anemia. Results from two small randomized studies produced conflicting results.
- C. Enrollment in a clinical trial should be considered for all patients with myelofibrosis-associated anemia.

VIII. POEMS syndrome

- A. Regimens used as systemic therapy for POEMS syndrome with widespread osteosclerotic lesions or bone marrow involvement are modelled after those used in other conditions, such as MM. There are limited data to guide choice in therapy.
- B. Case reports have demonstrated clinical improvement after treatment with lenalidomide (Revlimid) with or without dexamethasone. Two small, uncontrolled studies reported responses in over 70% with 60 to 75% progression free at three years.
- C. Thalidomide (Thalomid) has also shown activity but is associated with a less favorable side effect profile.
- D. Larger, well-controlled trials are needed to confirm the safety and efficacy of these agents for POEMS syndrome.

IX. Systemic light chain amyloidosis (AL)

- A. There is insufficient evidence to support the use of lenalidomide (Revlimid) or pomalidomide (Pomalyst) for the management of AL. Both medications are listed in NCCN guidelines among several other treatment options; however, the optimal treatment of the underlying plasma cell disorder has not been identified. Treatment of AL should be in the context of a clinical trial when possible.

References

1. Revlimid [Prescribing Information]. Summit, NJ: Celgene; October 2019.
2. Thalomid [Prescribing Information]. Summit, NJ: Celgene; October 2019.
3. Pomalyst [Prescribing Information]. Summit, NJ: Celgene; October 2019.
4. National Comprehensive Cancer Network. NCCN Guidelines: Multiple Myeloma v3.2020. Available at: http://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf (Accessed on April 06, 2020).
5. National Comprehensive Cancer Network. NCCN Guidelines: Myelodysplastic Syndrome v2.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/mds.pdf (Accessed on April 06, 2020).
6. National Comprehensive Cancer Network. NCCN Guidelines: B-Cell Lymphomas v1.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf (Accessed on April 06, 2020).
7. National Comprehensive Cancer Network. NCCN Guidelines: Myeloproliferative Neoplasms v3.2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf (accessed on April 06, 2020).
8. National Comprehensive Cancer Network. NCCN Guidelines: Systemic Light Chain Amyloidosis v1.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/amyloidosis.pdf (accessed on April 6, 2020).
9. National Comprehensive Cancer Network. NCCN Guidelines: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma v4.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf (Accessed on April 06, 2020).
10. Leonard JP, Trneny M, Izutsu K, et al. AUGMENT: A Phase III Study of Lenalidomide Plus Rituximab Versus Placebo Plus Rituximab in Relapsed or Refractory Indolent Lymphoma. J Clin Oncol. 2019;37(14):1188-1199.
11. Chanan-Khan A, Miller KC, Musial L, Lawrence D, Padmanabhan S, et al. Clinical efficacy of lenalidomide in patients with relapsed or refractory chronic lymphocytic leukemia: results of a phase II study. J Clin Oncol. 2006 Dec 1;24(34):5343-9.
12. Ferrajoli A, Lee BN, Schlette EJ, O'Brien SM, Gao H, et al. Lenalidomide induces complete and partial remissions in patients with relapsed and refractory chronic lymphocytic leukemia. Blood. 2008;111(11):5291-7.

13. Badoux XC, Keating MJ, Wen S, et al. Phase II study of lenalidomide and rituximab as salvage therapy for patients with relapsed or refractory chronic lymphocytic leukemia. *J Clin Oncol* 2013;31:584-591.
14. Wang M, Fowler N, Wagner-Bartak N, et al. Oral lenalidomide with rituximab in relapsed or refractory diffuse large cell, follicular, and transformed lymphoma: a phase II clinical trial. *Leukemia* 2013;27:1902-1909.
15. Czuczman MS, Trneny M, Davies A, et al. A phase 2/3 multicenter, randomized, open-label study to compare the efficacy and safety of lenalidomide versus investigator's choice in patients with relapsed or refractory diffuse large B-cell lymphoma. *Clin Cancer Res* 2017;23:4127-4137.
16. Ferreri AJ, Sassone M, Zaja F, et al. Lenalidomide maintenance in patients with relapsed diffuse large B-cell lymphoma who are not eligible for autologous stem cell transplantation: an open label, single-arm, multicentre phase 2 trial. *Lancet Haematol*. 2017;4(3):e137-e146.
17. Wiernik PH, Lossos IS, Tusciano JM, et al. Lenalidomide monotherapy in relapsed or refractory aggressive non-Hodgkin's lymphoma. *J Clin Oncol*. 2008;26(30):4952-7.
18. Jabbour E, Thomas D, Kantarjian H, et al. Comparison of thalidomide and lenalidomide as therapy for myelofibrosis. *Blood*. 2011;118(4):899-902.
19. Mesa RA, Yao X, Cripe LD, Li CY, Litzow M, et al. Lenalidomide and prednisone for myelofibrosis: Eastern Cooperative Oncology Group (ECOG) phase 2 trial E4903. *Blood*. 2010;116(22):4436-8. 24.
20. Daver N, Cortes J, Newberry K, et al. Ruxolitinib in combination with lenalidomide as therapy for patients with myelofibrosis. *Haematologica*. 2015;100(8):1058-63.
21. Santini V, Almeida A, Giagounidis A, et al. Randomized Phase III Study of Lenalidomide Versus Placebo in RBC Transfusion-Dependent Patients With Lower-Risk Non-del(5q) Myelodysplastic Syndromes and Ineligible for or Refractory to Erythropoiesis-Stimulating Agents. *J Clin Oncol*. 2016;34(25):2988-96.
22. Drug Facts and Comparisons. Facts & Comparisons® eAnswers [online]. 2012. Available from Wolters Kluwer Health, Inc. Accessed April 5, 2012.
23. Ruan J, Martin P, Shah B, et al. Lenalidomide plus rituximab as initial treatment of mantle-cell lymphoma. *N Engl J Med*. 2015;373:1835-1844.
24. Pomalidomide. In: DRUGDEX Evaluations. Greenwood Village (CO): Thomson Healthcare; 1974- 2013 [cited February 25, 2013]. Available from <http://thomsonhc.comwith subscription>.
25. Freedman AS. Treatment of relapsed or refractory mantle cell lymphoma. In: UpToDate, Lister A (Ed), UpToDate, Waltham, MA. (Accessed on February 05, 2020).
26. Rajkumar SV. Multiple myeloma: Regimens used for relapsed or refractory disease. In: UpToDate, Kyle RA (Ed), UpToDate, Waltham, MA. (Accessed on February 03, 2020).
27. Scollard DS. Leprosy: Treatment and prevention. In: UpToDate, von Reyn CF (Ed), UpToDate, Waltham, MA. (Accessed on February 07, 2020).
28. Schlenk RF, Stegelmann F, Reiter A, et al. Pomalidomide in myeloproliferative neoplasm-associated myelofibrosis. *Leukemia* 2017;31:889-895.
29. Tefferi A, Al-Ali HK, Barosi G, et al. A randomized study of pomalidomide vs placebo in person with myeloproliferative neoplasm-associated myelofibrosis and RBC-transfusion dependence. *Leukemia* 2017;31:896-902
30. Nozza A, Terenghi F, Gallia F, et al. Lenalidomide and dexamethasone in patients with POEMS syndrome: results of a prospective, open-label trial. *Br J Haematol*. 2017;179(5):748-755.
31. Li J, Huang XF, Cai QQ, et al. A prospective phase II study of low dose lenalidomide plus dexamethasone in patients with newly diagnosed polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome. *Am J Hematol*. 2018;93(6):803-809.
32. Rajkumar SV, Jacobus S, Callander NS, et al. Lenalidomide plus high-dose dexamethasone verses lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. *Lancet Oncol* 2010;11:29-37
33. List A, Dewald G, Bennett J, et al. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. *N Engl J Med* 2006;355:1456-1465
34. Raza A, Reeves JA, Feldman EJ, et al. Phase 2 study of lenalidomide in transfusion-dependent, low-risk, and intermediate-1 risk myelodysplastic syndromes with karyotypes other than deletion 5q. *Blood* 2008;111:86-93
35. Santini V, Almeida A, Giagounidis A, et al. Randomized phase III study of lenalidomide versus placebo in RBC transition-dependent patients with lower risk non-del(5q) myelodysplastic syndromes and ineligible for or refractory to erythropoiesis-stimulating agents. *J Clin Oncol* 2016;34:2988-2996
36. Hamuryudan V, Mat C, Saip S, et al. Thalidomide in the treatment of the mucocutaneous lesions of the Behçet syndrome. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med*. 1998;128(6):443-50.

37. Little RF, Wyvill KM, Pluda JM, et al. Activity of thalidomide in AIDS-related Kaposi's sarcoma. J Clin Oncol. 2000;18(13):2593-602.

Policy Implementation/Update:

Action and Summary of Changes	Date
Added generic lenalidomide to policy with requirement to step through generic lenalidomide prior to use of branded Revlimid	05/2023
Addition of new indication for Kaposi Sarcoma for Pomalyst as experimental and investigational	06/2020
- For multiple myeloma indications, updated language to clarify use as either monotherapy, or with dexamethasone as part of a double-drug or triple-drug regimen - Added CLL to the not medically necessary section - Added the following experimental/investigational indications: - As part of a quadruple regimen for MM - Systemic light chain amyloidosis - POEMS - Behçet syndrome	04/2020
Added pomalidomide (Pomalyst) and thalidomide (Thalomid) agents to policy; removed black box warnings and precautions readily available in compendia; removed laboratory criteria.	12/2019
Converted lenalidomide (Revlimid) to policy format. Added new indication of follicular lymphoma and marginal zone lymphoma. Allowed coverage as monotherapy in multiple myeloma maintenance following autologous hematopoietic stem cell transplant. Allowed a route to coverage in myelodysplastic syndromes without a deletion 5q abnormality following phase III trial data.	08/2019
Excluded package insert/monitoring question and removed renewal question regarding regular hematological laboratory tests, extended initial approval from 3 months to 6 months.	01/2018
Previous reviews	09/2012, 10/2012, 10/2014, 09/2015, 01/2016
Policy created	08/2012

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP282

Description

Leniolisib (Joenja) is an orally administered phosphoinositide 3-kinase delta (PI3Kδ) inhibitor.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
leniolisib (Joenja)	Activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS)	70 mg tablets	60 tablets/30 days

Initial Evaluation

- I. **Leniolisib (Joenja)** may be considered medically necessary when the following criteria are met:
 - A. Member is 12 years of age or older; **AND**
 - B. Member weighs ≥ 45 kg; **AND**
 - C. Medication is prescribed by, or in consultation with, an immunologist, geneticist, or a provider specializing in the management of immunodeficiencies; **AND**
 - D. Medication will not be used in combination with immunosuppressive therapy (e.g., B lymphocyte depletion therapy, rituximab); **AND**
 - E. A diagnosis of **Activated phosphoinositide 3-kinase delta (PI3Kδ) syndrome (APDS)** when the following are met:
 1. Documentation of APDS-associated mutation with pathogenic variants in PIK3CD or PIK3R1 genes; **AND**
 2. Documentation of at least one measurable enlarged lymph node lesion observed by computed tomography (CT scan) or magnetic resonance imaging (MRI scan); **AND**
 3. Documentation of baseline naïve B cell percentage as assessed by flow cytometry; **AND**
 4. Member has one of the following clinical findings and manifestations of APDS as documented in the medical records:
 - i. History of repeated infections (e.g., sinus, ear, or lung infections, herpes viral infection) requiring long-term antibiotic or antiviral prophylaxis; **OR**
 - ii. Organ dysfunction (e.g., bronchiectasis, liver impairment); **OR**
 - iii. History of nodal or extra-nodal lymphoproliferation; **AND**
 5. Treatment with one agent in each of the following classes has been ineffective, contraindicated, or not tolerated:
 - i. Systemic corticosteroids (e.g., prednisone, methylprednisolone, budesonide)

- ii. Immunoglobulin G (IgG) replacement therapy (IRT)
 - iii. Other immunosuppressants (e.g., rituximab, sirolimus)
- II. Leniolisib (Joenja) is considered investigational when used for all other conditions except APDS

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 immunosuppressive therapy (e.g., B lymphocyte depletion therapy, rituximab); **AND**
- IV. Documentation showing that the member has exhibited improvement or stability of disease symptoms as noted by one of the following:
 - Reduction in nodal or extra-nodal lymphoproliferation (lymph node size) from pre-treatment baseline
 - Increase in naïve B cell percentage from pre-treatment baseline

Supporting Evidence

- I. Leniolisib (Joenja) is a phosphoinositide 3-kinase delta (PI3Kδ) inhibitor FDA-approved for the treatment of activated phosphoinositide 3-kinase delta syndrome (APDS) in adult and pediatric patients (≥ 12 years of age). It is available as a 70 mg oral tablet administered twice daily. Use in patients under the age of 12 has not yet shown safety and efficacy.
- II. The recommended dosage of leniolisib (Joenja) in adult and pediatric patients 12 years of age and older, weighing 45 kg or greater, is 70 mg administered orally twice daily approximately 12 hours apart, with or without food. There is no recommended dosage for patients weighing less than 45 kg.
- III. APDS is a rare primary immunodeficiency caused by mutations in PIK3CD or PIK3R1 genes, characterized by severe, recurrent sinopulmonary infections, lymphoproliferation, bronchiectasis, cytopenias, and may progress to permanent lung damage or lymphoma. APDS affects approximately 1 to 2 persons per million in the US. Given the rarity and complexity of diagnosis and management of APDS, the treatment of APDS must be initiated by, or in consultation with, an immunologist, geneticist, or a provider specializing in the management of immunodeficiencies.
- IV. Leniolisib (Joenja) was evaluated for the treatment of APDS via a clinical trial, which enrolled patients with nodal and/or extranodal lymphoproliferation, as measured by index nodal lesion selected by the Cheson methodology on CT or MRI and clinical findings and manifestations compatible with APDS (e.g., history of repeated oto-sino-pulmonary infections, organ dysfunction). Immunosuppressive medications or PI3Kδ inhibitors (selective or non-selective) were prohibited within 6 weeks of baseline (Day -1 and the visit prior to first study drug administration) and throughout the study. In addition, patients who had previous or concurrent B cell depleters (e.g., rituximab) within 6 months of baseline were excluded from the study,

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unless absolute B lymphocytes in the blood were normal. B cell depleters were prohibited throughout the study. At this time, safety, and efficacy of leniolisib (Joenja) in combination with B cell depleting immunosuppressive therapy (e.g., rituximab) is not known. Additionally, the proposed therapeutic goal for the use of leniolisib (Joenja) is to improve the naïve B lymphocyte counts. Use of B cell depleting therapies may antagonize the effect of leniolisib (Joenja).

- V. In the absence of curative treatments, management of APDS is symptom-based and consists of non-specific therapies including ongoing antimicrobial prophylaxis, immunosuppressants (e.g., corticosteroids, rituximab, sirolimus), immunoglobulin replacement therapy (IRT), surgeries (e.g., tonsillectomy, splenectomy), and hematopoietic stem cell transplant (HSCT).
- VI. There are no treatment guidelines for the management of APDS and the pharmacotherapy approaches remain patient-specific and heterogeneous. Leniolisib (Joenja) is the first targeted PI3K δ inhibitor, and the first drug FDA-approved for the treatment of APDS. Leniolisib (Joenja) is expected to be the first-line therapy for all patients with a confirmed diagnosis of APDS with other therapeutic interventions (e.g., antibiotics, IRT, corticosteroids) being utilized as adjunct therapies.
- VII. The safety and efficacy of leniolisib (Joenja) were evaluated in a Phase 3, blinded, randomized, placebo controlled clinical trial (Study 2201-02). Patients (N=31): 12 to 75 years old with mutation in PIK3CD or PIK3R1, a history of clinical symptoms of APDS, and at least one measurable lymph node enlargement, were randomized 2:1 to receive leniolisib (Joenja) or placebo. While concurrent use of immunosuppressants was prohibited during the trial, patients were allowed to take glucocorticoids (e.g., prednisone) $\leq$ 25 mg per day (58%) and previously established IRT (68%). The negative change in the index lymph node diameters and the positive change in the naïve B cells percentage (baseline to day 85) were measured as co-primary endpoints. Leniolisib (Joenja) treatment for 85 days reported a baseline mean log₁₀-sum of product diameter (SPD) reductions in the index lesions (lymph nodes) of -0.27 for leniolisib (Joenja) versus -0.02 for placebo (treatment difference of -0.25 (95%CI, -0.38, -0.12; p 0.0006). Additionally, the change in naïve B cell percentage from baseline to day 85 (only assessed in patients who had <48% baseline naïve B cells, and who were not censored during trial; n=13) showed a 37.39% increase in naïve B cell percentage in the treatment group versus a 0.09% increase in placebo (p 0.0002).
- VIII. The analysis of naïve B cell percent improvement was confounded due to the censoring of 13 patients from the treatment group and five from the placebo group (protocol deviations, $\geq$ 48% naïve B cells at baseline, and lack of baseline or day 85 data). However, in a supportive analysis inclusive of all patients (excluding those without baseline or day 85 measurements), the naïve B cells percentage improvement was consistent and showed a mean difference between leniolisib (Joenja, n = 13) and placebo (n = 8) at 27.94% (95% CI: 15.02, 40.85; p 0.0003).
- IX. Key and exploratory secondary outcomes such as improvements in spleen size, autoimmune cytopenia, and patient-reported quality of life (SF-36) at 12 weeks were not statistically significant; however, showed a favorable trend toward leniolisib (Joenja).
- X. A single-arm, open-label extension (OLE) trial (N=35) for leniolisib (Joenja) did not report additional safety signals. Further reduction of SPD of index lesions and spleen volume were reported as well as up to 32% increase in naïve B cells with up to 252 days of treatment. These outcomes remain observational. During OLE, the patient reported QoL measures (mean change from baseline of the SF-36 and the WPAI-CIQ) remained unchanged. Additionally, study participants continued to receive antibiotics at a similar rate as those in Study 2201-02.

- XI. The quality of evidence is considered low. Although objective measures, the changes in SPD index lesions and naïve B cells have not been validated or correlated with clinically meaningful outcomes in APDS such as patients' quality of life, reduction in infections, bronchiectasis, and incidence of lymphoma or death. Study 2201-02 had a small sample size, a short outcome assessment time frame, and a confounded data set due to the censoring of patients as well as the allowance of concurrent use of systemic corticosteroids and IRT. Although indicative of short-term benefits; significant hesitancy remains when considering the long-term application and the true effect of leniolisib (Joenja). Further clinical trials may help elucidate the efficacy and confirmation of the benefit of leniolisib (Joenja).
- XII. Leniolisib (Joenja) is currently being evaluated in a Phase 3 trial in children aged four to 11 years.
- XIII. Based on treatment exposure in all participants (N=31), adverse events (AEs) were reported by 85.7% of patients in leniolisib (Joenja) and in 90.0% in the placebo group; most commonly grade 1 (74.2%). Serious AEs were reported in five (16%) patients, none of whom were ascribed to the study drug. The most common AE in the treatment arm versus placebo included headache (24% vs 20%), sinusitis (19% vs 0%), and atopic dermatitis (14% vs 0%).
- XIV. There were no treatment discontinuations or deaths during the clinical trial. Although no contraindications are listed, the leniolisib (Joenja) label includes warnings related to embryo-fetal toxicity. The real-world safety profile of leniolisib (Joenja) remains undetermined.
- XV. Due to the lack of long-term efficacy data, and the low confidence in the clinically meaningful outcomes in APDS, true efficacy benefits and place in therapy for leniolisib (Joenja) remain relatively uncertain. Although expected to be a first-line agent, majority of the APDS patients may remain candidates for standard-of-care front-line therapies such as antibiotic and antiviral prophylaxis, use of systemic corticosteroids, Immunoglobulin G (IgG) replacement therapy (IRT), and other immunosuppressants (e.g., rituximab, sirolimus). Given the long-term safety, efficacy, real-world practice experience and therapy cost, these agents may remain practical alternatives to leniolisib (Joenja).

Investigational or Not Medically Necessary Uses

- I. Leniolisib (Joenja) has not been FDA-approved, or sufficiently studied for safety and efficacy for any other condition(s) than APDS

References

1. Rao VK, Webster S, et al. A randomized, placebo-controlled phase 3 trial of the PI3Kδ inhibitor leniolisib for activated PI3Kδ syndrome. *Blood*. 2023 Mar 2;141(9):971-983.
2. Joenja (leniolisib). Package Insert. Pharming Healthcare Inc, Warren NJ. March 2023.
3. Coulter TI, Cant AJ. The Treatment of Activated PI3Kδ Syndrome. *Front Immunol*. 2018 Sep 7;9: 2043.

Related Policies

Currently, there are no related policies.

Policy Implementation/Update:

Policy Implementation/Update:	Date
Policy created	08/2023

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP130

Description

Lettermovir (Prevymis) is an orally administered antiviral agent that inhibits cytomegalovirus (CMV) deoxyribonucleic acid (DNA) terminase complex which helps prevent CMV infection in adult and pediatric CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT) who are 6 months or older and weight ≥ 6 kg and adult and pediatric CMV-seronegative recipients of a kidney transplant from a seropositive donor [D+/R-] who are 12 years or older and weight ≥ 40 kg.

Length of Authorization

- Initial: up to 200 days post-transplant
- Renewal: no renewal

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
letermovir (Prevymis)	240 mg tablet	Prophylaxis for CMV Infection Post-HSCT and Kidney Transplant	28 tablets/28 days
	480 mg tablet		
	20 mg pellet packets		120 packets/30 days
	120 mg pellet packets		120 packets/30 days

Initial Evaluation

- I. **Lettermovir (Prevymis)** may be considered medically necessary when the following criteria below are met:
 - A. Medication is prescribed by, or in consultation with, an oncologist, hematologist, infectious disease, or transplant specialist; **AND**
 - B. Member will be using letermovir (Prevymis) for the prevention of CMV infection or disease; **AND**
 - C. Provider attestation that member is at high risk of CMV infection; **AND**
 - D. A diagnosis of one of the following:
 1. **Allogeneic hematopoietic stem cell transplant (HSCT); AND**
 - i. Member is 6 months of age or older; **AND**
 - ii. Documented weight of ≥ 6 kg; **AND**
 - iii. Member is cytomegalovirus (CMV)-seropositive HSCT recipient; **AND**
 - iv. Documentation of transplant date has been recorded in chart notes; **AND**
 - v. Provider attestation that letermovir (Prevymis) will not be used past 100-days post-transplant; **OR**
 - a. If patient is at high-risk for late CMV infection, provider attests that letermovir (Prevymis) will not be used past 200-days post-transplant; **AND**

- i. Member has received, or will receive, letermovir (Prevymis) as primary prophylaxis during the first 100-days post-transplant; **OR**

2. Kidney transplant; AND

- i. Member is 12 years of age or older; **AND**
 - ii. Documented weight of ≥ 40 kg; **AND**
 - iii. Member is a CMV-seronegative kidney transplant recipient; **AND**
 - iv. Kidney donor is CMV-seropositive; **AND**
 - v. Documentation of transplant date has been recorded in chart notes; **AND**
 - vi. Provider attestation that letermovir (Prevymis) will be initiated between days 0 and 7 post-transplant; **AND**
 - vii. Provider attestation that letermovir (Prevymis) will not be used past 200 days post-transplant; **AND**
 - viii. Member has an intolerance or contraindication to valganciclovir
- II. Letermovir (Prevymis) is considered investigational when used for all other conditions, including but not limited to:
- A. Prevention of CMV infection or disease settings other than HSCT or kidney transplant
 - B. Treatment for CMV infection or disease
 - C. Prevention of CMV infection beyond 200 days post-transplant
 - D. Pre-emptive therapy of CMV infection

Supporting Evidence

- I. Letermovir (Prevymis) is only FDA-approved in the setting of CMV prophylaxis in adults and pediatric CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT) who are 6 months or older and weigh ≥ 6 kg and adult and pediatric CMV-seronegative recipients of a kidney transplant from a CMV-seropositive donor [D+/R-] who are 12 years or older and weight ≥ 40 kg.
- II. Considering the complexity of care for patients receiving HSCT or kidney transplant, the agent requested must be prescribed by, or in consultation with, an oncologist, hematologist, infectious disease, or transplant specialist.
- III. The recommended dose of letermovir (Prevymis) according to the prescribing information is 480mg daily in adults. If letermovir (Prevymis) is intended to be used in combination with cyclosporine as part of anti-rejection regimen, the dose of letermovir (Prevymis) should be reduced to 240mg daily due to a drug-drug interaction that causes an increase in serum blood concentrations of both drugs. Dosing recommendations in pediatric patients are based on the patient's weight and dose reductions are recommended for those receiving in combination with cyclosporine.
- IV. **Allogeneic hematopoietic stem cell transplant (HSCT)**
 - The safety and efficacy of letermovir (Prevymis) was studied in a multicenter, double-blind, placebo-controlled, Phase 3 trial in adult CMV-seropositive recipients [R+] of those who have received an allogeneic hematopoietic stem cell transplant (HSCT). Of the 325 participants who received letermovir (Prevymis), 38% failed prophylaxis compared to 61% in the placebo arm [95% CI (32.5, 14.6)].

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- A review by Chen et al. 2018 demonstrated that among the six antiviral therapies studied, ganciclovir and letermovir (Prevymis) were the most effective in reducing incidence of CMV reactivation when used as universal prophylaxis agents. Results further suggest that patients undergoing allogeneic HSCT would significantly benefit from universal prophylaxis with an agent that is tolerable after HSCT. The data suggest that although effective at reducing CMV reactivation and disease, ganciclovir use cannot be recommended as a universal prophylaxis agent because of an increased risk of myelosuppression and subsequent drug discontinuation. In contrast, the data suggests that letermovir (Prevymis) has an excellent safety profile with no myelosuppression, and its use should be considered for this indication in patients at risk. Letermovir (Prevymis) was associated with a decrease in CMV-related outcomes and all-cause mortality through 24 weeks after HSCT. Data around acyclovir found that although a delay in the onset of CMV reactivation was demonstrated, acyclovir showed nonsignificant efficacy in preventing CMV disease. Valacyclovir, which has a greater bioavailability than acyclovir was compared with acyclovir and found to be associated with a lower rate of viremia with similar rate of survival to acyclovir in CMV R+ or D+ allogeneic HCT recipients. High-dose acyclovir and valacyclovir are less myelosuppressive than ganciclovir and appear to have some efficacy for CMV prophylaxis, but these agents have inferior in vitro activity against CMV than ganciclovir. Though ganciclovir has promising efficacy, treatment is limited in this HSCT patient due to its increased risk of myelosuppression.
- Extended use of letermovir (Prevymis) post-HSCT up to 200 days was studied in a randomized, double-blind, placebo-controlled, phase 3 clinical trial of 218 patients who had been treated with 100-days of primary prophylaxis with letermovir (Prevymis). The primary efficacy endpoint of percentage of patients with clinically significant CMV infection from week 14 (~100 days) post-transplant through week 28 (~200 days) post-transplant was experienced in 2.8% of patients in the letermovir (Prevymis) group compared to 18.9% of patients in the placebo group (-16.1, 95% CI [-25.8 to -6.5]; p-value = 0.0005). Reported adverse events were in alignment with those reported in the pivotal clinical trials and no new safety concerns were observed.
- Patients enrolled in the extended use trial had high risk of CMV disease, and the prescribing information for letermovir (Prevymis) indicates that extended use up to 200 days post-transplant can be used in patients at risk for late CMV infection and disease. IDSA guidelines suggest that risk factors for late onset CMV disease include [D+/R-] serostatus, shorter courses of prophylaxis, higher levels of immunosuppression, and allograft rejection (i.e., graft versus host disease [GVHD]).

V. Kidney Transplant

- Letermovir (Prevymis) was evaluated in a randomized, active-controlled, double-masked, double-dummy, non-inferiority trial in 601 patients who were CMV-seronegative recipients of a kidney transplant from a CMV-seropositive donor [D+/R-]. Patients were randomized to receive letermovir (Prevymis) or valganciclovir (VGCV) for 28 weeks and were observed for 52 weeks. The primary efficacy outcome was incidence of CMV disease through week 52, which was exhibited in

10.4% of patients in the letermovir (Prevymis) group and 11.8% of patients in the VGCV group (stratum-adjusted difference, -1.4% [95% CI, -6.5% to 3.8%]). Notably, no patients in the letermovir (Prevymis) group developed CMV disease through week 28 compared to 5 patients (1.7%) in the VGCV group (stratum-adjusted difference, -1.7% [95% CI, -3.4% to 0.1%]).

- The most commonly reported adverse events in the letermovir group were diarrhea (31.5%), tremor (18.2%), and urinary tract infection (14%), while the most common adverse event leading to discontinuation were neutropenia (1%) and leukopenia (1%). However, drug-related leukopenia and neutropenia occurred less often in the letermovir (Prevymis) group (11.3% and 2.7%, respectively) than in the VGCV group (37.0% and 16.5%, respectively). The safety profile of letermovir (Prevymis) appears to be favorable compared to VGCV.
- The Infectious Disease Society of America (IDSA) and Transplant Society guidelines on the management of CMV in solid organ transplant indicate that standard of care for CMV prevention in kidney transplant patients is extended use (200 days) of either ganciclovir (GCV) or VGCV. However, extended use of VGCV has been associated with higher rates of myelosuppression, manifesting primarily as leukopenia and neutropenia. Letermovir (Prevymis) may be considered appropriate in patients who are at a higher risk of myelosuppression given its favorable safety profile and observed lower risk of myelotoxicity.
- According to the prescribing information for letermovir (Prevymis), therapy should be initiated during the first week post-transplant and continued through day 200 post-transplant for all kidney transplant recipients.

VI. Pediatric use of Prevymis for CMV prophylaxis in allogenic HSCT and kidney transplants

- Safety and efficacy for use in pediatric patients was approved and established by a Phase 2, open-label, single-arm pharmacokinetics study where participants received letermovir once daily within 28 days post allogenic HSCT through week 14 (approximately 100 days). Dose was based on age, weight and whether they are taking concomitant cyclosporine.
- The study included pediatric participants from birth to <18 years of age. Sixty-three participants were divided into 3 age groups [(group 1: 12 to <18 years; n=28); (group 2: 2 to <12 years; n=27); (group 3: birth to <2 years; n=8)]. Baseline characteristics include a median age of 11 years and 70% male.
- Pharmacokinetic outcomes found that medications levels across all 3 age groups and dosing regimens were comparable to adult letermovir exposure levels. Fifty-six participants were included in the efficacy review and there were 11 failures at week 14 (19.6%) and 14 failures through week 24 (25%).
- All participants were included in the safety analysis and adverse event rates were comparable across all age groups. The most common adverse events were vomiting (58.7%), pyrexia (42.9%), diarrhea (38.1%), GVHD (38.1%), nausea (28.6%), abdominal pain (28.6%). Drug-related AEs were determined to be vomiting (17.5%) and nausea (3.2%). No new safety events occurred as compared to the adult studies.

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 below:
 - A. Prevention of CMV infection or disease settings other than HSCT or kidney transplant
 - B. Treatment for CMV infection or disease
 - C. Prevention of CMV infection beyond 200 days post-transplant
 - D. Pre-emptive therapy of CMV infection

Appendix

- I. Recommended Daily Oral Dosage of Prevmis in Pediatric HSCT Recipients 6 months to less than 12 years of age or 12 years of age and older weighing less than 30kg

Body Weight	Daily Oral Dose	Tablets	Oral Pellets
30 kg and above	480 mg	One 480 mg tablet or two 240mg tablets	Four 120 mg packets of oral pellets
15 kg to less than 30 kg	240 mg	One 240 mg tablet	Two 120 mg packets of oral pellets
7.5 kg to less than 15 kg	120 mg	Not recommended	One 120 mg packets of oral pellets
6 kg to less than 7.5 kg	80 mg	Not recommended	Four 20 mg packets of oral pellets

- II. Recommended Dosage of Prevmis when co-administered with cyclosporine in pediatric HSCT recipients 6 months to less than 12 years of age or 12 years of age and older and weighing less than 30 kg

Body Weight	Daily Oral Dose	Tablets	Oral Pellets
30 kg and above	240 mg	One 240 mg tablet	Two 120 mg packets of oral pellets
15 kg to less than 30 kg	120 mg	Not recommended	One 120 mg packets of oral pellets
7.5 kg to less than 15 kg	60 mg	Not recommended	Three 20 mg packets of oral pellets
6 kg to less than 7.5 kg	40 mg	Not recommended	Two 20 mg packets of oral pellets

References

1. Prevmis [Prescribing Information]. Whitehouse Station, NJ: MERCK & CO, Inc. January 2025.
2. Chen K, Cheng MP, Hammond SP, et al. Antiviral Prophylaxis for Cytomegalovirus Infection in Allogeneic Hematopoietic Cell Transplantation. Blood Adv. 2018 Aug 28; 2(16): 2159–2175. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6113617/>
3. UpToDate, Inc. Prevention of viral infections in hematopoietic cell transplant recipients. UpToDate [database online]. Waltham, MA. Last updated August 28, 2023. Available at: <http://www.uptodate.com/home/index.html>.
4. Kotton CN, Kumar D, Caliendo AM, et al. The Third International Consensus Guidelines on the Management of Cytomegalovirus in Solid-organ Transplantation. Transplantation. 2018;102(6):900-931. doi:10.1097/TP.0000000000002191
5. Haidar G, Boeckh M, Singh N. Cytomegalovirus Infection in Solid Organ and Hematopoietic Cell Transplantation: State of Evidence. The Journal of Infectious Diseases. 2020;221(S1):S23-31.

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6. Limaye AP, Budde K, Humar A, et al. Letermovir vs Valganciclovir for Prophylaxis of Cytomegalovirus in High-Risk Kidney Transplant Recipients: A Randomized Clinical Trial. JAMA. 2023;330(1):33-42. doi:10.1001/jama.2023.9106
7. Groll AH, Danziger-Isakov L, Gefen A, et al. Cytomegalovirus prophylaxis with letermovir in pediatric (birth to <18 years of age) hematopoietic cell transplant recipients: pharmacokinetics, efficacy, and safety results of a Phase 2b study. Antimicrob Agents Chemother. Published online August 18, 2025. doi:10.1128/aac.00420-25

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated age requirement from 18 years old to 6 years in HSCT and 12 years in kidney transplant. Updated QL table and supporting evidence. Added dosing appendix	10/2025
Added criteria for extended use post-HSCT and kidney transplant indications; Updated supporting evidence	09/2023
Removed requirement of valganciclovir or ganciclovir trial given reduced efficacy and/or safety in comparison to letermovir	10/2020
Policy created	11/2019

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP044

Description

Levodopa (Inbrija) is an orally inhaled metabolic precursor to dopamine used to relieve symptoms of Parkinson's disease.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
levodopa (Inbrija)	42 mg capsules	Parkinson's Disease	120 capsules/30 days*

*Maximally allowed does upon clinical review for medical necessity: 300 capsules/30 days

Initial Evaluation

- I. Levodopa (Inbrija) may be considered medically necessary when the following criteria below are met:
 - A. Prescribed by, or in consultation with, a neurologist; **AND**
 - B. Not used in combination with apomorphine (Apokyn, Kynmobi); **AND**
 - C. Documentation that member does **not** have a diagnosis of chronic respiratory disease (e.g. COPD, asthma, etc.); **AND**
 - D. A diagnosis of **Parkinson's Disease (PD)** when the following are met:
 1. Documentation that the member has moderate to severe Parkinson's disease symptoms; **AND**
 2. Is currently on an oral levodopa regimen at least 3 times a day for a minimum of 2 weeks prior to starting levodopa (Inbrija); **AND**
 3. Documentation that the member has a decrease in wearing off symptoms in response to the member's usual morning dose of levodopa; **AND**
 4. Prescriber attest that member will be using levodopa (Inbrija) in combination with carbidopa/levodopa; **AND**
 5. The quantity requested is 120 capsules per 30 days; **OR**
 - i. Documentation of medical necessity for dose escalation; **AND**
 - ii. Attestation that the member has been taught how to prepare and use the inhaler system appropriately; **AND**
 - iii. Attestation that the member is able to administer the full dose of levodopa (Inbrija); **AND**
 6. Treatment with the following has been ineffective, contraindicated or not tolerated:
 - i. Carbidopa/levodopa IR up to five times a day OR carbidopa/levodopa XR; **AND**

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- ii. ONE of the following:
 - a. Dopamine agonist (e.g. pramipexole, ropinirole, rotigotine)
 - b. monoamine oxidase –B (MAO-B) inhibitor (e.g. selegiline, rasagiline, safinamide)
 - c. Catechol-O-methyl transferase (COMT) inhibitors (e.g. entacapone, tolcapone).
- II. Levodopa (Inbrija) is considered investigational when used for all other conditions, including but not limited to:
 - A. Mild Parkinson’s disease symptoms
 - B. Parkinson’s disease WITHOUT documentation of motor fluctuations, “wearing off” phenomenon

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. Prescriber attests that member will be using levodopa (Inbrija) in combination with carbidopa/levodopa ; **AND**
- IV. Documentation that member has a reduction in wearing off period from baseline

Supporting Evidence

- I. Moderate to severe Parkinson’s disease symptoms were defined in the pivotal SPAMSM-PD trial as a modified Hoehn and Yahr (H&Y) rating 22 of stages 1-3 in the ON state and recognizable, predictable OFF episodes totaling ≥2 hours per day (excluding early-morning OFF time).
- II. A UPDRS Part III score of ≥ 25% after the patient’s usual morning dose of levodopa reflects that the patient’s wearing off motor symptoms are responsive to levodopa treatment.
- III. Patients who were taking apomorphine (Apokyn) were excluded from the SPAMSM-PD trial
- IV. Due to the safety concerns, patients with chronic respiratory disease are excluded from the SPAMSM-PD trial.
- V. Levodopa (Inbrija) has only been shown to be effective in combination with carbidopa/levodopa.
- VI. According to the American Family Physician diagnosis and treatment guideline for Parkinson’s disease, the treatment algorithm for motor complication is:
 - Fractionate carbidopa/levodopa therapy five times a day and consider adding a dopamine agonist, MAO-B inhibitor, OR COMT inhibitor.
- VII. Levodopa (Inbrija) has not been studied in patients with mild Parkinson’s disease or Parkinson’s disease without motor fluctuations; therefore, it would be considered investigational when Inbrija is requested in those settings.

References

1. Inbrija [Prescribing Information]. Acorda Therapeutics: Ardsley, NY. December 2018.
2. LeWitt P, Hauser RA, Pahwa R, et al. Safety and efficacy of CVT-301 (levodopa inhalation powder) on motor function during off periods in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet Neurol*. 2019 Feb;18(2):145-154. doi: 10.1016/S1474-4422(18)30405-8.
3. UpToDate, Inc. Motor fluctuations and dyskinesia in Parkinson disease. UpToDate [Online Database]. Waltham, MA. Last updated July 12, 2018. Available from: <http://uptodate.com/home/index.html>. Accessed February 11, 2019.
4. Rao S., M.D., Hofmann L., M.D., and Shakil A., M.D. Parkinson's Disease: Diagnosis and Treatment. University of Texas Southwestern Medical School at Dallas Family Medicine Residency Program, Dallas, Texas. *Am Fam Physician*. 2006 Dec 15;74(12):2046-2054.

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated formatting of QL table, improved clarity of policy requirement around previous agents trialed, added renewal requirement of continuing carbidopa/levodopa, and removed renewal requirement of 'absence of unacceptable toxicities.' Addition of new standard renewal language noting previous approvals and member is not continuing via samples.	04/2021
Policy Created	05/2019

Policy Type: PA

Pharmacy Coverage Policy: UMP195

Description

Lofexidine (Lucemyra) is an orally administered alpha-2 adrenergic agonist.

Length of Authorization

- Initial: 14 days
- Renewal: cannot be renewed

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
lofexidine (Lucemyra)	0.18 mg tablets	Mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults	224 tablets/14 days
generic lofexidine	0.18 mg tablets	Mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults	224 tablets/14 days

Initial Evaluation

- I. **Lofexidine (Lucemyra)** may be considered medically necessary when the following criteria are met:
 - A. Member is 18 years of age or older; **AND**
 - B. Member will NOT be transitioned to buprenorphine or methadone; **AND**
 - C. Member will initiate therapy with naltrexone (Vivitrol) **prior** to lofexidine (Lucemyra) course completion; **AND**
 - D. Total duration of therapy will not exceed 14 days; **AND**
 - E. Request is for generic lofexidine; **OR**
 1. If request is for brand Lucemyra, generic lofexidine has been ineffective, not tolerated, or is contraindicated; **AND**
 - F. A diagnosis of **treatment for opioid use disorder needing withdrawal from opioid use** when the following are met:
 1. History of use with clonidine; **AND**
 2. History of use with tizanidine; **OR**
 3. Documentation of clinical rationale for why tizanidine AND clonidine is not medically appropriate
- II. Lofexidine (Lucemyra) is considered not medically necessary when criteria above are not met and/or when used for:
 - A. Treatment transition to buprenorphine or methadone
 - B. Treatment duration longer than 14 days

- III. Lofexidine (Lucemyra) is considered investigational when used for all other conditions, including but not limited to:
- A. Use for marijuana dependence
 - B. Use for heroin dependence
 - C. Acute opioid withdrawal symptoms

Supporting Evidence

- I. A retrospective clinical review by Gregory and colleagues reviewed the use of a three-drug regimen including tizanidine, gabapentin, and hydroxyzine for the mitigation of withdrawal symptoms in 84 patients. Primary outcomes were completion of a medically supervised withdrawal and initiation of injectable extended release (ER) naltrexone treatment. Results showed that 94% of patients completed the medically supervised withdrawal phase, and 89% successfully transitioned to ER naltrexone.
- II. Use of lofexidine (Lucemyra), in combination with an opioid agonist or partial agonist, for the treatment of opioid withdrawal symptoms increases the risk of QT interval and/or reduces the efficacy of either therapy. Combination use is considered not medically necessary.

Investigational or Not Medically Necessary Uses

- I. Lofexidine (Lucemyra) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Use for marijuana dependence
 - B. Use for heroin dependence
 - C. Acute opioid withdrawal symptoms

References

1. Lucemyra [Prescribing Information]. Louisville, KY: US WorldMeds, LLC. November 2019.
2. Gregory Rudolf, Jim Walsh, Abigail Plawman, Paul Gianutsos, William Alto, Lloyd Mancl & Vania Rudolf (2018) A novel non-opioid protocol for medically supervised opioid withdrawal and transition to antagonist treatment, The American Journal of Drug and Alcohol Abuse, 44:3, 302-309.

Policy Implementation/Update:

Action and Summary of Changes	Date
Added generic lofexidine to QL table, and added criteria to prefer generic formulation	09/2024
Transitioned to policy format	10/2020
Previous Reviews	07/2018

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP131

Description

Lomitapide (Juxtapid) is a microsomal triglyceride transfer protein inhibitor used to reduce low density lipoprotein-cholesterol (LDL-C) in patients with homozygous familial hypercholesterolemia (HoFH).

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
lomitapide (Juxtapid)	5 mg capsules	Homozygous familial hypercholesterolemia (HoFH)	30 capsules /30 days
	10 mg capsules		
	20 mg capsules		
	30 mg capsules		
	40 mg capsules		
	60 mg capsules		

Initial Evaluation

- I. Lomitapide (Juxtapid) 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 cardiologist, endocrinologist or lipid specialist; **AND**
 - C. Member has a diagnosis of **homozygous familial hypercholesterolemia (HoFH)** as confirmed by one of the following:
 1. Genetic confirmation of two mutant alleles at the LDLR, Apo-B, PCSK9, or ARH adaptor protein 1/LDLRAP1 gene locus; **OR**
 2. Untreated LDL-C >500 mg/dL; **OR**
 3. Treated LDL-C ≥ 300 mg/dL with one of the following:
 - i. Cutaneous or tendon xanthoma before ten years of age; **OR**
 - ii. History of heterozygous familial hypercholesterolemia (HeFH) in both parents; **AND**
 - D. Member will be on concurrent treatment with a high dose statin **plus** another lipid lowering therapy (e.g. ezetimibe, fibrate, nicotinic acid, LDL-apheresis) unless all are contraindicated, or not tolerated; **AND**
 - E. Treatment with a PCSK-9 inhibitor [e.g. alirocumab (Praluent), evolocumab (Repatha)] has been ineffective, contraindicated, or not tolerated

- II. Lomitapide (Juxtapid) is considered investigational when used in combination with a PCSK9 inhibitor, and 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. Absence of unacceptable toxicity from the medication. Examples of unacceptable toxicity may include, but are not limited to: elevations in transaminases (i.e. ALT, AST), hepatic steatosis with or without concomitant increases in transaminases; **AND**
- IV. Member continues to receive other lipid-lowering therapy (e.g. statin, ezetimibe); **AND**
- V. Clinical documentation (e.g. chart notes, laboratory values) confirming reduction of LDL-C while on therapy; **AND**
- VI. Medication will not be used in combination with a PCSK9 inhibitor

Supporting Evidence

- I. Lomitapide (Juxtapid) is indicated for the treatment of HoFH, a genetic disease marked by very high LDL-C levels.
- II. The diagnosis of HoFH is made with genetic testing or clinical criteria.
 - A causative mutation in the LDLR, APOB, or PCSK9 gene(s) confirms a HoFH diagnosis.
 - Criteria for a clinical diagnosis according to the Simon Broome Register Group, include untreated LDL-C >500 mg/dL, treated LDL-C ≥300 mg/dL, cutaneous or tendon xanthoma before age 10 years, or elevated LDL-C levels consistent with heterozygous FH in both parents.
- III. All patients in the pivotal clinical trial for lomitapide (Juxtapid) met diagnostic criteria for HoFH based either on clinical criteria or on documented mutation(s) in both alleles of the LDL receptor or of genes known to affect LDL receptor function.
- IV. The safety and efficacy of lomitapide (Juxtapid) for HoFH was evaluated in an open-label, Phase 3, non-randomized, dose-escalating study. The study included 29 adult patients with HoFH where the majority of patients received concurrent high-dose statin and more than half underwent regular apheresis. After 26 weeks of treatment the LDL-C was reduced by about 50% from baseline (336 to 166 mg/dL).
- V. The safety and efficacy of lomitapide (Juxtapid) has not been established in pediatric patients.
- VI. The effect of lomitapide (Juxtapid) on cardiovascular morbidity and mortality has not been determined.
- VII. Due to the risk of hepatotoxicity, lomitapide (Juxtapid) has a REMS program to ensure safe and appropriate use, thereby limiting distribution to only certified healthcare providers and pharmacies. The requirements of the program include: limiting use to patients with a clinical or laboratory diagnosis of HoFH, excluding pregnancy and those with significant hepatic impairment (Child-Pugh B or C). Additional, elements of the program emphasize close

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monitoring of hepatic function and patient education regarding a low-fat diet. Further information is available at www.JUXTAPIDREMSProgram.com.

- VIII. Besides lomitapide (Juxtapid), other treatment options for HoFH include evolocumab (Repatha), LDL-apheresis, and standard lipid-lowering agents (e.g. statins, ezetimibe); however, treatment with these agents should be an adjunct to diet and exercise.

Investigational or Not Medically Necessary Uses

- I. The benefit of lomitapide (Juxtapid) for indications outside of HoFH have not been established and may not outweigh the rare, but serious adverse events. The FDA approved labeling for lomitapide (Juxtapid) specifically states that it should not be used in patients with hypercholesterolemia who do not have HoFH due to the lack of safety and efficacy outside of this setting.
- II. The safety and efficacy of these agents have not been established in combination with PCSK9 inhibitors.

References

1. Juxtapid [Prescribing Information]. Cambridge, MA: Aegerion Pharmaceuticals; August 2017
2. Cuchel, M, Meagher, EA, du Toit Theron, H, et al. Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study. *Lancet*. 2013 Jan 5;381(9860):40-6. PMID: 23122768
3. FDA Approved Risk Evaluation and Mitigation Strategies (REMS): lomitapide (Juxtapid). From: <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm?event=IndvRemsDetails.page&REMS=25>
4. Rosenson, RS. Familial hypercholesterolemia in adults: Overview. In: UpToDate. Saperia, GM (Ed), UpToDate, Waltham, MA, 2019
5. Rosenson, RS. Treatment of drug-resistant hypercholesterolemia. In: UpToDate, Saperia, GM (Ed), UpToDate, Waltham, MA, 2019

Policy Implementation/Update:

Date Created	May 2013
Date Effective	May 2013
Last Updated	December 2019
Last Reviewed	11/2015, 12/2019

Action and Summary of Changes	Date
- Transitioned to policy format - Removed mipomersen (Kynamro) from policy due to discontinuation status as of 5/31/2018 - Added requirement for specialty prescriber - Added minimum age requirement - Added details regarding confirmation of a diagnosis of HoFH - Clarified that use must be concurrent with standard lipid-lowering agents - Indicated that combination of lomitapide (Juxtapid) with PCSK9 inhibitors or use for hypercholesterolemia without HoFH is considered investigational	12/2019

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP227

Description

Lonafarnib (Zokinvy) is a farnesyltransferase inhibitor.

Length of Authorization

- Initial: Four months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
lonafarnib (Zokinvy)	50 mg capsules	Hutchinson-Gilford Progeria Syndrome (HGPS); processing-deficient Progeroid Laminopathies (PL)	Initial: Maximum 230mg/m ² /day
	75 mg capsules		Renewal: Maximum 300mg/m ² /day

Initial Evaluation

- I. Lonafarnib (Zokinvy) may be considered medically necessary when the following criteria are met:
 - A. Member is one year of age or older; **AND**
 - B. Medication is prescribed by, or in consultation with, a pediatrician or specialist in progeroid syndromes, genetics, or metabolic disorders; **AND**
 - C. Documentation of members body surface area (BSA); **AND**
 - D. Member has a BSA of 0.39m² or greater; **AND**
 - E. Provider attestation the member's cardiovascular status will be monitored [e.g., carotid-femoral pulse wave velocity (PWVcf), carotid artery ultrasonography]; **AND**
 - F. A diagnosis of one of the following:
 1. **Hutchinson-Gilford Progeria Syndrome (HGPS); AND**
 - i. Member has genetic test confirmation of a lamin A gene mutation; **OR**
 2. **Processing-deficient Progeroid Laminopathies (PL); AND**
 - i. Member has genetic test confirmation of:
 - a. Heterozygous LMNA mutation with progerin-like protein accumulation; **OR**
 - b. Homozygous or compound heterozygous ZMPSTE24 mutations.
- II. Lonafarnib (Zokinvy) is considered experimental and investigational when criteria above are not met and/or when used for:

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- A. Processing-proficient Progeroid Laminopathies
- B. Other than above mentioned Progeroid Syndromes
 - i. Wiedemann-Rautenstrauch syndrome
 - ii. Werner syndrome
 - iii. Bloom syndrome
 - iv. Rothmund-Thomson syndrome
 - v. Cockayne syndrome, xeroderma pigmentosum and trichothiodystrophy
 - vi. Fanconi anaemia
 - vii. Seckel syndrome
 - viii. Ataxia telangiectasia
 - ix. Dyskeratosis congenita and Hoyeraal-Hreidarsson 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. Medication is prescribed by, or in consultation with, a pediatrician or specialist in progeroid syndromes, genetics or metabolic disorders; **AND**
- IV. Documentation of members body surface area (BSA) measured in the past three months; **AND**
- V.** Provider attests the member has exhibited improvement or stability of disease symptoms [e.g., cardiovascular status (e.g., carotid-femoral pulse wave velocity (PWVcf), carotid artery ultrasonography), bone mineral density].

Supporting Evidence

- I. The safety and efficacy of lonafarnib (Zokinvy) has not been studied in pediatric patients less than 12 months of age. The activity of cytochrome P450 (CYP)3A4 and CYP3A5 is low in newborns, approximately 5% to 15% of that of an adult and only achieves full activity at six months of age. Considering these enzymes play a key role in the metabolism of lonafarnib (Zokinvy), it is expected that the clearance would be reduced and there is an increased risk of commonly observed treatment emergent adverse events (TEAEs).
- II. The safety and efficacy of lonafarnib (Zokinvy) has only been studied in patients with the body surface area (BSA) ranging from 0.38 m² to 0.75 m². Due to the lack of clinical trial data on safety and efficacy, and unknown dosage strength, it is not indicated in patients with the BSA less than 0.39m².
- III. Hutchinson-Gilford Progeria Syndrome (HPS) and processing-deficient PLs are rare and fatal genetic diseases. Considering the complexity of the disease state it is necessary for lonafarnib (Zokinvy) to be prescribed by or in consultation with a specialist in progeroid syndromes, genetics, or metabolic disorders.
- IV. Patients with HGPS and processing-deficient PLs experience hypertension, strokes, angina, enlarged heart, and heart failure. Progressive atherosclerosis is common, generally leading to

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death from myocardial infarction or stroke at the age of approximately 15 years. It is crucial to monitor the cardiovascular status [e.g., carotid-femoral pulse wave velocity (PWVcf), carotid artery ultrasonography]. In a study that sought to better understand cardiovascular disease associated with HGPS, elevated PWVcf, increased intima-media and adventitia echodensity, abnormal ABL, and increased ICA mean flow velocity were identified as pervasive disease features in HGPS. Researchers noted that non-invasive measures including PWVcf, carotid wall echodensity and ICA flow velocity offer quantitative insights into accelerated vasculopathy with HGPS and may therefore, provide indicators of disease progression or remission with therapies.

- V. The safety and efficacy of lonafarnib (Zokinvy) have been studied in a observational cohort survival study, which retrospectively compared survival data from two, open-label, single-arm, Phase 2 trials (Study 1 and Study 2) in 62 patients to those from a natural history cohort in 62 patients with HGPS.
- The primary efficacy outcome was all-cause mortality. Among the 62 patients in the treatment group four died (6.3%) and among the 62 patients in the matched untreated group 17 died (27%). None of these deaths were considered by investigators to be treatment related.
 - Through the first three years of follow up, the mean lifespan of HGPS patients treated with lonafarnib increased by three months, and increased by two and a half years through the last follow-up time (11 years) compared to untreated patients.
 - Study 1 included 28 patients (26 with classic HGPS, one with non-classic HGPS, and one with processing-deficient PL with an LMNA heterozygous mutation). Treatment was initiated with 115mg/m² twice daily and after four months of treatment patients who were tolerating treatment had a dose increase to 150 mg/m² twice daily.
 - The primary efficacy endpoint of the achievement of at least a 50% increase in the annual rate of weight gain over the rate documented at study entry by the study team, was met by eleven of 28 patients (39.3%).
 - The secondary outcome was change in carotid artery ultrasonography and corrected PWVcf. Echodensity of the carotid artery intima media (10th and 50th percentile), adventitia deep near wall (10th and 50th percentile), and adventitia luminal near wall (50th percentile) all decreased statistically significantly from baseline to end of therapy (all p<0.05). PWVcf improved with a median percent decrease from baseline of 15.3% (range: -43.6%, 34.1%; p=0.0028).
 - Study 2 consisted of two phases. In the first phase patients received lonafarnib (Zokinvy) in conjunction with zoledronic acid and pravastatin for five years. In the second phase patients received lonafarnib (Zokinvy) at a dose of 150mg/m² twice daily for three years.
 - The study enrolled 26 patients from Study 1 and 13 treatment naïve patients.
 - The primary efficacy endpoint of weight gain (at least 10% increase in the annual rate) or echodensity was met by 22 (71%) of patients.
 - The most common adverse reactions (≥25%) in the clinical trials were vomiting, diarrhea, infection, nausea, decreased appetite, fatigue, upper respiratory tract infection, abdominal pain, musculoskeletal pain, electrolyte abnormalities, decreased weight, headache, myelosuppression, increased aspartate aminotransferase, decreased blood bicarbonate, cough, hypertension, and increased alanine aminotransferase

- VI. Progeroid laminopathies (PLs) are due to various mutations either in the LMNA gene and/or the ZMPSTE24 gene. The processing-deficient PLs are specifically due to heterozygous LMNA mutation with progerin-like protein accumulation or homozygous or compound heterozygous ZMPSTE24 mutations. These conditions are more rare than HGPS, and were underrepresented in the clinical trials.

Investigational or Not Medically Necessary Uses

- I. Lonafarnib (Zokinvy) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Progeroid syndromes (Wiedemann-Rautenstrauch syndrome, Werner syndrome, Bloom syndrome, Rothmund-Thomson syndrome, Cockayne syndrome, xeroderma pigmentosum and trichothiodystrophy, Fanconi anaemia, Seckel syndrome, Ataxia telangiectasia, Dyskeratosis congenita and Hoyerlaal-Hreidarsson syndrome) are a group of very rare genetic disorders that are characterized by clinical features that mimic physiological ageing, such as hair loss, short stature, skin tightness, cardiovascular diseases and osteoporosis. But considering the mechanism of action, lonafarnib (Zokinvy) would not be effective in these populations.
 - B. Processing-proficient Progeroid Laminopathies – considering the pathophysiology of the disease state and the mechanism of action, lonafarnib (Zokinvy) would not be effective in these populations.

References

1. Zokinvy [Prescribing Information]. Eiger BioPharmaceuticals: Palo Alto, CA. November 2020.
2. Leslie B Gordon, MD, PhD, et.al. Hutchinson-Gilford Progeria Syndrome. GeneReviews. 2003.
3. Gordon LB, et al. Clinical trial of a farnesyltransferase inhibitor in children with Hutchinson-Gilford progeria syndrome. Proc Natl Acad Sci U S A. 2012;109(41):16666-16671. doi:10.1073/pnas.1202529109
4. Gordon LB, et al. Clinical Trial of the Protein Farnesylation Inhibitors Lonafarnib, Pravastatin, and Zoledronic Acid in Children With Hutchinson-Gilford Progeria Syndrome. Circulation. 2016;134(2):114-125. doi:10.1161/CIRCULATIONAHA.116.022188
5. Gordon LB, et al. Association of Lonafarnib Treatment vs No Treatment With Mortality Rate in Patients With Hutchinson-Gilford Progeria Syndrome. JAMA. 2018;319(16):1687-1695. doi:10.1001/jama.2018.3264
6. Dido Carrero, et al. Hallmarks of progeroid syndromes: lessons from mice and reprogrammed cells. Disease Models & Mechanisms 2016 9: 719-735; doi: 10.1242/dmm.024711
7. Anderson BJ, Larsson P. A maturation model for midazolam clearance. Paediatr Anaesth. 2011 Mar;21(3):302-8.
8. Kodidela S, et al. Developmental pattern of hepatic drug-metabolizing enzymes in pediatric population and its role in optimal drug treatment. Arch Med Health Sci. 2017;5:115-22.
9. Gordon LB, et al. Hutchinson-Gilford Progeria Syndrome. GeneReviews. 2019. Available online: <https://www.ncbi.nlm.nih.gov/books/NBK1121/>.
10. Gerhard-Herman M, Smoot LB, Wake N, et al. Mechanisms of premature vascular aging in children with Hutchinson Gilford progeria syndrome. Hypertension. 2012 January ; 59(1): 92–97. doi:10.1161/HYPERTENSIONAHA.111.180919.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2021

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP052

Description

Granulocyte-colony stimulating factors (G-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
pegfilgrastim (Neulasta)	6 mg/0.6 mL prefilled syringe	Prophylactic use in patients with non-myeloid malignancy; Neutropenic complications from prior chemotherapy cycle; Exposure to myelosuppressive doses of radiation;	Two prefilled syringes per 28-day supply
pegfilgrastim (Neulasta Onpro)	6 mg/0.6 mL prefilled syringe with on-body injector kit		Two kits per 28-day supply
pegfilgrastim-cbqv (Udenyca)	6 mg/0.6 mL prefilled syringe		Two prefilled syringes per 28-day supply
	6 mg/0.6 mL autoinjector		Two autoinjectors per 28-day supply
pegfilgrastim-cbqv (Udenyca ON-BODY)	6 mg/0.6 mL prefilled syringe co-packaged with the on-body injector		2 prefilled syringe co-packaged with the on-body injector/28 days
pegfilgrastim-jmdb (Fulphila)*	6 mg/0.6 mL prefilled syringe	Bone marrow transplantation failure or engraftment delay; Peripheral progenitor cell (PBPC) mobilization and transplant Warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome†	Two prefilled syringes per 28-day supply
pegfilgrastim-bmez (Ziextenzo)			
pegfilgrastim-apgf (Nyvepria)*			
pegfilgrastim-pbbk (Fylnetra)			
pegfilgrastim-fpgk (Stimufend)			

* There is no prior authorization required for pegfilgrastim-apgf (Nyvepria) and pegfilgrastim-jmdb (Fulphila) 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. **Pegfilgrastim (Neulasta, Neulasta Onpro), pegfilgrastim-cbqv (Udenyca, Udenyca On-body), pegfilgrastim-pbbk (Fylnetra), pegfilgrastim-bmez (Ziextenzo), and pegfilgrastim-fpgk (Stimufend)** may be considered medically necessary when the following criteria below are met:

pegfilgrastim-apgf (Nyvepria) and pegfilgrastim-jmdb (Fulphila) are the preferred long-acting G-CSF

- **Patients must have failed, or have a contraindication, or intolerance to pegfilgrastim-apgf (Nyvepria) AND pegfilgrastim-jmdb (Fulphila) prior to consideration of any other long-acting G-CSF**

There is no prior authorization required for pegfilgrastim-apgf (Nyvepria) or pegfilgrastim-jmdb (Fulphila) unless requesting above the quantity limit noted above.

- A. Treatment with pegfilgrastim-jmdb (Fulphila) AND pegfilgrastim-apgf (Nyvepria) have been ineffective, contraindicated, or not tolerated; **AND**
- B. A diagnosis of the following:
1. **Peripheral Blood Progenitor Cell (PBPC) mobilization and transplant; OR**
 2. **A neutropenic complication from a prior cycle of the same chemotherapy; OR**
 3. **Bone Marrow Transplantation (BMT) failure or Engraftment Delay; OR**
 4. **Member acutely exposed to myelosuppressive doses of radiation (Hematopoietic Subsyndrome of Acute Radiation Syndrome); OR**
 5. **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:
 - a. Age 65 years or older AND receiving full dose intensity chemotherapy; **OR**
 - b. History of recurrent febrile neutropenia from chemotherapy; **OR**
 - c. Extensive prior exposure to chemotherapy; **OR**
 - d. Previous exposure of pelvis, or other areas of large amounts of bone marrow, to radiation; **OR**
 - e. Pre-existing neutropenia (ANC $\leq$ 1000/mm³) or bone marrow involvement with tumor; **OR**
 - f. Member has a condition that can potentially increase the risk of serious infection (e.g. HIV/AIDS) ; **OR**
 - g. Infection/open wounds; **OR**
 - h. Recent surgery; **OR**
 - i. Poor performance status; **OR**
 - j. Poor renal function (creatinine clearance $<$ 50mL/min) ; **OR**
 - k. Liver dysfunction (elevated bilirubin $>$ 2.0mg/dL) ; **OR**
 - l. Chronic immunosuppression in the post-transplant setting including organ transplant.
 6. **Warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome; AND**

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- 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**
- iii. Documentation of absolute neutrophil count (ANC) <1500 cells/μL that is not related to medication, chemotherapy, or secondary to viral infection

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 pegfilgrastim as once per chemotherapy cycle, but no sooner than 14 days before and 24 hours after chemotherapy administration. Generally, chemotherapy is administered every 2-3 weeks, whereby frequency of pegfilgrastim is not expected to be more often than every two weeks. There are insufficient data to support use of weekly pegfilgrastim. For other indications, such as transplant and WHIM syndrome, therapy is continued until adequate neutrophil recovery is achieved. Accordingly, quantity exceptions may be considered when frequent administration of pegfilgrastim is deemed medically necessary.
- III. Duration of approval is based on usual duration of chemotherapy or radiation therapy cycles. 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. 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. 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.

- VI. 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 mavorixafor (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.
- VII. 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.
- VIII. 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.
- IX. 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

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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 biosimilars pegfilgrastim-apgf (Nyvepria) and pegfilgrastim-jmdb (Fulphila) is required prior to approval of non-preferred pegfilgrastim products.

References

1. Neulasta [Prescribing Information]. Amgen Inc. Thousand Oaks, CA. February 2021.
2. Fulphila [Prescribing Information]. Mylan GmbH. Zurich, Switzerland. June 2018.
3. Udenyca [Prescribing Information]. Coherus Biosciences, Inc. Redwood City, CA. April 2019.
4. Ziextenzo [Prescribing Information]. Sandoz Inc. Princeton, NJ. November 2019.
5. Nyvepria [Prescribing Information]. Hospira, Inc., a Pfizer Company. Lake Forest, IL. October 2021.
6. Fylmetra [Prescribing Information]. Kashiv BioSciences, LLC. Piscataway, NJ. May 2022.
7. Stimufend [Prescribing Information]. Fresenius Kabi USA, LLC. Lake Zurich, IL. September 2022.
8. Smith TJ, Bohlke K, Lyman GH, et al. Recommendations for the use of wbc growth factors: American Society of Clinical Oncology clinical practice guideline update. JCO. 2015;33(28):3199-3212.
9. Wisconsin Physicians Service Insurance Corporation. Local Coverage Determination (LCD): Human Granulocyte/Macrophage Colony Stimulating Factors (L34699). Centers for Medicare & Medicaid Services, Inc. Updated on 1/23/2018 with effective date 02/1/2018. Accessed March 2018.
10. First Coast Service Options, Inc. Local Coverage Determination (LCD): G-CSF (Neupogen®, Granix™, Zarxio™) (L34002). Centers for Medicare & Medicaid Services, Inc. Updated on 6/10/2016 with effective date 7/5/2016. Accessed March 2018.
11. National Government Services, Inc. Local Coverage Article: Filgrastim, Pegfilgrastim, Tbofilgrastim, Filgrastim-sndz (e.g., Neupogen®, Neulasta™, Granix™, Zarxio™) - Related to LCD L33394 (A52408). Centers for Medicare & Medicaid Services, Inc. Updated on 9/23/2016 with effective date 10/1/2016. Accessed March 2018.
12. Palmetto GBA. Local Coverage Determination: White Cell Colony Stimulating Factors (L37176). Centers for Medicare & Medicaid Services, Inc. Updated on 12/7/2017 with effective date 2/26/2018. Accessed March 2018.
13. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology for Hematopoietic Growth Factors, Version 1.2022. Updated December 22, 2021.
14. U.S. Food and Drug Administration. Biosimilars – Healthcare provider materials. Updated July 28, 2021. https://www.fda.gov/drugs/biosimilars/health-care-provider-materials?utm_campaign=cder-factsheets&utm_content=&utm_medium=social&utm_source=linkedin
15. Biologics and Biosimilars Collective Intelligence Consortium. Biosimilar facts. <https://www.bbcic.org/resources/biosimilars-facts>
16. Dale DC, Bonilla MA, Davis MW, et al. A randomized controlled phase III trial of recombinant human granulocyte colony-stimulating factor (filgrastim) for treatment of severe chronic neutropenia. *Blood*. 1993;81(10):2496-2502.
17. National Organization for Rare Diseases (NORD). WHIM Syndrome. January 16, 2024. Accessed May 23, 2024. <https://rarediseases.org/rare-diseases/whim-syndrome>

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
Short-acting Granulocyte-colony stimulating factor (CSF) and Granulocyte macrophage-CSF (GM-CSF)	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 cycle
	Acute myeloid leukemia (AML) patient following induction or consolidation chemotherapy
	Bone marrow transplantation failure or engraftment delay

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	Severe chronic neutropenia
	Myelodysplastic syndrome
	Exposure to myelosuppressive doses of radiation
Mavorixafor (Xolremdi)	WHIM syndrome

Policy Implementation/Update:

Action and Summary of Changes	Date
Added pathway to coverage in the setting of WHIM syndrome. Updated supporting evidence, quantity limits table, references, and related policies sections.	08/2024
Added Udenyca On-Body to the policy	04/2024
Updated policy to reflect new preferred product strategy (pegfilgrastim-apgf (Nyvepria) and pegfilgrastim-jmdb (Fulphila) [Effective 01/01/2024]	12/2023
Added Udenyca autoinjector to QL table	03/2023
Added new product pegfilgrastim-fpgk (Stimufend) after trial of pegfilgrastim-jmdb (Fulphila) AND pegfilgrastim-bmez (Ziextenzo)	09/2022
Updated policy supporting evidence and references. Added related policies table. Added new product Fylnetra (pegfilgrastim-pbbk) after trial of pegfilgrastim-jmdb (Fulphila) AND pegfilgrastim-bmez (Ziextenzo)	08/2022
Updated policy name from “pegfilgrastim (Neulasta®; Neulasta Onpro®; Fulphila®; Udenyca®; Ziextenzo®, Nyvepria™)” to “Long-acting Granulocyte colony stimulating factor”	04/2022
Updated pegfilgrastim-jmdb (Fulphila) as preferred product; removed pegfilgrastim-cbqv (Udenyca) from preferred products. (Effective 7/1/2021)	05/2021
Updated preferred products to add Ziextenzo (effective 1/1/2021) and move Neulasta/Neulasta Onpro to non-preferred (effective 1/1/2021). Added Nyvepria, biosimilar to Neulasta.	11/2020
Updated policy to allow for 28 days supply	02/2020
Added Ziextenzo, biosimilar to Neulasta; update quantity limits to allow for 30 days supply	12/2019
Added Udenyca, biosimilar to Neulasta	01/2019
Neulasta, Neulasta Onpro preferred GCSF	12/2018
Added Fulphila, biosimilar to Neulasta	07/2018
Policy created	02/2018

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP249

Description

Maribavir (Livtency) is an orally administered benzimidazole riboside.

Length of Authorization

- Initial: Eight weeks
- Renewal: Eight weeks

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
maribavir (Livtency)	200 mg tablets	Post-transplant CMV infection/disease that is refractory to other treatments	112 tablets/28 days

Initial Evaluation

- I. **Maribavir (Livtency)** 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, an oncologist, hematologist, infectious disease, or transplant specialist; **AND**
 - C. Medication is prescribed for the treatment of cytomegalovirus (CMV) infection or disease; **AND**
 1. Member is seropositive for CMV; **AND**
 2. Member has received a solid organ transplant (SOT) or hematopoietic stem cell transplant (HSCT); **AND**
 3. Medication will not be used in combination with other medications for CMV (e.g., valganciclovir, ganciclovir, foscarnet, cidofovir, letermovir [Prevymis]); **AND**
 4. The member is resistant or refractory to at least one of the following medications, unless all are contraindicated;
 - i. Valganciclovir
 - ii. Ganciclovir
 - iii. Foscarnet
 - iv. Cidofovir
- II. Maribavir (Livtency) is considered not medically necessary when criteria above are not met and/or when used for:
 - A. CMV infection that is not resistant or refractory to other conventional therapies (e.g., valganciclovir, ganciclovir, foscarnet, cidofovir)

- III. Maribavir (Livtency) is considered investigational when used for all other conditions, including but not limited to:
- A. Maribavir (Livtency) used in combination with other CMV therapies
 - B. CMV prophylaxis
 - C. HIV AIDS-related CMV

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 is prescribed by, or in consultation with, an oncologist, hematologist, infectious disease or transplant specialist; **AND**
- IV. Medication is prescribed for cytomegalovirus (CMV) infection or disease; **AND**
 - A. Provider attests to all of the following:
 - a. Member experienced a positive response to an initial treatment course, as indicated by CMV viremia clearance or resolution of CMV disease symptoms; **AND**
 - b. There has been a gap in therapy following the initial eight-week treatment course; **AND**
 - c. A blood and/or plasma test has been completed, showing an increase in CMV viremia level following the end of the last treatment course of maribavir (Livtency); **AND**
 - d. Testing has been done, following the most recent treatment course, confirming the member is not resistant to maribavir (Livtency)

Supporting Evidence

- I. Cytomegalovirus (CMV) is an infection associated with immunosuppression. In the setting of solid organ transplant (SOT) and hematopoietic stem cell transplant (HSCT), CMV is a serious complication. Patients may experience CMV syndrome (e.g., fever, malaise, myalgias, arthralgias, leukopenia, thrombocytopenia), end-organ disease (retinitis, pneumonitis, hepatitis), and mortality. CMV infection is a significant risk factor for mortality, development of graft vs. host disease, graft loss, and organ dysfunction if not treated appropriately. Therapy for CMV is complex and may be administered prophylactically, preemptively, or may be reserved for the treatment of CMV syndrome or disease. Treatment approach varies depending on transplant type, serostatus, risk profile, and organ function; thus, management and oversight from a specialist to guide and monitor therapy is warranted.
- II. Ganciclovir (IV), valganciclovir, foscarnet (IV), and cidofovir (IV) are used off-label for post-transplant CMV, and have known safety and efficacy; however, all target viral protein UL54, and are susceptible to cross resistance. Maribavir (Livtency) is a benzimidazole riboside with inhibition against UL97 that has activity and efficacy in patients that are resistant to conventional therapies. It is FDA-approved for post-transplant CMV infection/disease in those resistant or refractory to at least one conventional therapy.

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- III. Maribavir (Livtency) was evaluated in a pivotal Phase 3 clinical trial that was a randomized, open-label study against investigator assigned therapy (IAT) for eight weeks. Patients were adults with confirmed CMV viremia, were resistant or refractory to one or more conventional therapies (i.e., ganciclovir, valganciclovir, foscarnet, cidofovir), and had received HSCT or SOT. The clinical trial allowed enrollment of patients 12 years of age and older; however, no patients under the age of 18 enrolled in the trial. Maribavir (Livtency) is FDA-approved for patients 12 years of age and older (weighing at least 35 kg). The exposure of drug therapy is expected to be similar to that of adult patients, and support for use in patients 12-18 years of age is based on the fact that course of disease is expected to be similar in pediatric and adult populations and pharmacokinetic data indicates drug exposure is expected to be similar. Use of therapy in the 12-18 age population likely has benefits that outweigh the risks given patients will be resistant/refractory to other treatment options.
- IV. Maribavir (Livtency) showed statistical and clinical superiority to the IAT treatment arm in CMV DNA levels at the end of eight weeks of treatment, as well as maintenance of treatment effect at week 16 (with an eight-week treatment free period following the eight weeks of therapy). There was no difference in all-cause mortality. Limitations of the clinical trial were the high discontinuation rate in the IAT treatment arm and variety of regimens included in the IAT treatment arm. This limits the ability to conclude true superiority of maribavir (Livtency) over any or all conventional therapies, notably in the refractory population. It is predicted that maribavir (Livtency) would be superior in those that are resistant to conventional therapies; however, the population included in the trial was a mix of patients that were resistant and refractory. Of note, therapy has not been correlated with a survival benefit, and for the majority of patients this medication does not maintain clearance long-term (i.e., beyond 16 weeks after treatment initiation with an eight-week therapy course). There is a high rate of CMV recurrence, partially due to resistance. Virologic relapse generally occurs four-to-eight weeks after treatment discontinuation. Furthermore, use of therapy in the first-line setting may confer resistance to valganciclovir and ganciclovir, and may then limit available effective treatment options in the second-line setting.
- V. It is unknown if maribavir (Livtency) will be efficacious in the prophylactic setting or outside of post-transplant related CMV infection. There are other medications FDA-approved and recommended in these settings. Use of conventional therapies, and guidance from treatment guidelines should be followed as untreated or inappropriately treated CMV may lead to serious complications including graft-loss and/or mortality. Confirmed CMV viremia via seropositive status is indicative of CMV infection, and should be confirmed prior to use of this therapy. Maribavir (Livtency) continues to be evaluated in the first-line setting (not relapsed or refractory); however, given the known safety, efficacy, ability to overcome UL54 resistance, and cost effectiveness of conventional agents, maribavir (Livtency) should be reserved for the relapsed/refractory population. Although the safety profile of maribavir (Livtency) differs from that of conventional therapies, conventional therapies (e.g., valganciclovir, ganciclovir, foscarnet, cidofovir) should be considered for all patients that lack contraindication to them given extensive clinical experience, more established safety profile, and cost effectiveness. The known adverse effects from valganciclovir, ganciclovir, foscarnet, and cidofovir are predictable and have known management strategies to mitigate toxicities and maximize treatment. In the setting of contraindication to all conventional therapies (i.e., valganciclovir, ganciclovir, foscarnet, and cidofovir), treatment with maribavir (Livtency) is a reasonable option. In a Phase 2 clinical trial, therapy showed efficacy, as well as a similar safety profile compared to the Phase 3 pivotal trial for the relapsed/refractory population. A Phase 3 trial is underway to confirm.

- VI. Maribavir (Livtency) has not been evaluated in combination with other CMV therapies. When used in combination with therapies such as valganciclovir and ganciclovir, maribavir (Livtency) may antagonize the effects of other medications. Given the reduced efficacy and potential additive safety concerns, concomitant use is not allowed.
- VII. Maribavir (Livtency) was evaluated for an eight-week treatment course in clinical trials. Safety and efficacy with a longer course of therapy has not been evaluated. It is unknown at this time if extended therapy would impact duration of viremia clearance and/or reduce the rate/risk of recurrence; thus, duration of therapy is limited to that which has shown clinical value in controlled clinical trials. A favorable response to therapy includes clearance of CMV DNA (<137 IU/mL), or a significant reduction in CMV DNA coupled with resolution and/or improvement in CMV disease symptoms. If adherence is achieved, failure to meet these treatment goals is indicative of resistance or refractory to maribavir (Livtency). After eight weeks of therapy, maribavir (Livtency) should be discontinued and patients should have a gap in therapy to determine success of treatment. If CMV DNA levels rapidly increase following an eight-week treatment course, further therapy may be warranted. Subsequent treatment courses of maribavir (Livtency) have not been evaluated for safety and efficacy; however, retreatment could be reasonable if an initial treatment course was successful, there are rapidly increasing CMV DNA levels following a prior successful treatment course, and if resistance testing has been done which indicates the patient has not conferred resistance to maribavir (Livtency). Similar to conventional treatment options, maribavir (Livtency) has a high rate of resistance, and resistance mutations result in failure to meet CMV viremia clearance.

Investigational or Not Medically Necessary Uses

- I. Maribavir (Livtency) is considered not medically necessary for treatment of CMV in the first-line setting given availability of several conventional treatment options with known efficacy, known safety profile, and superior cost-effectiveness. Therapy should ideally be reserved for patients with UL54 resistance, as maribavir (Livtency) has the ability to overcome this; however, if maribavir (Livtency) is utilized as a first-line treatment, UL97 resistance-associated substitutions may confer cross-resistance to ganciclovir and valganciclovir rendering fewer effective treatment options in the second-line setting.
- II. Maribavir (Livtency) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Maribavir (Livtency) used in combination with other CMV therapies
 - B. CMV prophylaxis
 - C. HIV AIDS-related CMV

References

1. Sundberg A, Alain S, Avery R, et al. A phase 3 active-controlled study of maribavir for the treatment of transplant recipients with refractory/resistant cytomegalovirus: study design. Poster presented at Transplantation & Cellular Therapy Meetings; February 19-23, 2020; Orlando, FL.
2. Maertens J, Cordonnier C, Jaksch P, et al. Maribavir for pre-emptive treatment of cytomegalovirus reactivation. *N Engl Med.* 2019;381(12): 1136-1147.
3. Papanicolaou GA, Silveira FP, Langston AA, et al. Maribavir for refractory or resistant cytomegalovirus infections in hematopoietic-cell or solid-organ transplant recipients: a randomized, dose-ranging, double-blind, phase 2 study. *Clin Infect Dis.* 2019;68(8):1255-1264.

4. Kotton CN, Kumar D, Caliendo AM, et al. The third international consensus guidelines on the management of cytomegalovirus in solid-organ transplantation. *Transplantation*. 2018;102(6):900-931.
5. Razonable RR, Humar A. Cytomegalovirus in solid organ transplant recipients-guidelines of the american society of transplantation infectious diseases community of practice. *Clin Transplant*. 2019;33(9):e13512.
6. Livtency [Prescribing Information]. Takeda Pharmaceuticals, Lexington, MA. November 2021.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	02/2022

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP316

Description

Marstacimab (Hypavzi) is a subcutaneous tissue factor pathway inhibitor (TFPI) antagonist.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
marstacimab (Hypavzi)	Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients 12 years of age and older with Hemophilia A or Hemophilia B without factor inhibitors	150 mg/mL prefilled pen	First Month: 5 pens (5 mL)/28 days Maintenance: 4 pens (4 mL)/ 28 days
			Maintenance (dose escalation): 8 pens (8 mL)/ 28 days*

*When dose escalation criteria are met

Initial Evaluation

- I. **Marstacimab (Hypavzi)** 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 hematologist; **AND**
 - C. Medication will not be used in combination with other agents for routine prophylaxis [e.g., factor replacement (Advate, Eloctate, BeneFIX, etc.), bypassing agent (NovoSeven, FEIBA, Sevenfact), non-factor replacement therapy (emicizumab-kxwh (Hemlibra)), etc.]; **AND**
 - D. Marstacimab (Hypavzi) will be used as routine prophylaxis to reduce the frequency of bleeding episodes; **AND**
 - E. Clinical documentation confirming that the member does not have history of inhibitors [i.e., documented high-titer inhibitor (≥ 5 BU/mL)]; **AND**
 - F. A diagnosis of one of the following:
 1. **Hemophilia A; AND**
 - i. Member has severe hemophilia A (defined as factor VIII level of $<1\%$); **OR**
 - a. Member has had two or more documented episodes of spontaneous bleeding; **AND**
 - ii. Clinical documentation that prior prophylaxis with factor VIII (e.g., Advate, Eloctate, Nuwiq, etc.) was ineffective for prevention of bleeding episodes; **AND**
 - iii. Clinical documentation of intolerance or contraindication to emicizumab-kxwh (Hemlibra); **OR**

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2. Hemophilia B; **AND**

- i. Member has moderate to severe hemophilia B (defined as factor IX level of less than or equal to 5%); **OR**
 - a. Member has had two or more documented episode of spontaneous bleeding; **AND**
 - ii. Clinical documentation that prior prophylaxis with factor IX (e.g., BeneFIX, Idelvion, etc.) was ineffective for the prevention of bleeding episodes
- II. Marstacimab (Hypmavzi) is considered investigational when used for all other conditions, including but not limited to:
- A. Marstacimab (Hypmavzi) used in combination with other agents for routine prophylaxis [e.g., factor replacement (Advate, Eloctate, BeneFIX, etc.), bypassing agent (NovoSeven, FEIBA, Sevenfact), non-factor replacement therapy (emicizumab-kxwh (Hemlibra)), etc.]
 - B. Pediatric patients <12 years of age with hemophilia A or B
 - C. Hemophilia A with inhibitors
 - D. Hemophilia B with inhibitors
 - E. Mild-to-moderate hemophilia A (Factor activity level $\geq 1\%$ of normal and $< 40\%$ of normal (≥ 0.01 and < 0.40 IU/mL)
 - F. Mild hemophilia B (Factor activity level $> 5\%$ of normal and $< 40\%$ of normal (> 0.05 and < 0.40 IU/mL)
 - G. Von Willebrand 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 (e.g., decreased incidence of bleeding episodes or stability of bleeding episodes relative to baseline); **AND**
- IV. Medication will not be used in combination with other agents for routine prophylaxis [i.e., factor replacement (Advate, Eloctate, BeneFIX, etc.), bypassing agent (NovoSeven, FEIBA, Sevenfact), non-factor replacement therapy (emicizumab-kxwh (Hemlibra)), etc.]; **AND**
- V. If the request is for marstacimab (Hypmavzi) dose escalation to 300 mg per week:
 - A. Member has demonstrated an initial response to therapy at a dose of 150 mg weekly (i.e., decreased incidence of bleeding episodes or stability of bleeding episodes relative to baseline); **AND**
 - B. Current weight is greater than or equal to 50 kg; **AND**
 - C. Member has experienced two or more breakthrough bleeds while on marstacimab (Hypmavzi) 150 mg weekly; **AND**
 - D. Dose escalation must not exceed 300 mg per week.

Supporting Evidence

- I. Marstacimab (Hypavzi) is a tissue factor pathway inhibitor (TFPI) antagonist FDA-approved for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in patients 12 years of age and older with hemophilia A and B without inhibitors. Tissue factor pathway inhibitor (TFPI) is an anticoagulation protein that regulates the extrinsic coagulation cascade by inactivating the protease functions of FXa/FVIIa/TF complex. When TFPI activity is blocked, the extrinsic coagulation cascade continues to work without requiring amplification by FVIII/FIX whose normal plasma levels are reduced in hemophilia.
- II. The efficacy and safety of marstacimab (Hypavzi) has not been studied in a pediatric population less than 12 years of age. Current FDA approval is limited to those 12 years of age and older.
- III. Hemophilia A (factor VIII deficiency) and hemophilia B (factor IX) are X-linked inherited coagulation factor deficiencies that result in lifelong bleeding disorders. The availability of factor replacement products has dramatically improved care for those with hemophilia A and B. The severity of an individual's hemophilia is determined by the amount of clotting factor present. Plasma levels of FVIII or FIX < 40% are indicative of hemophilia; however, hemophilia A and B are classified moderate when factor levels are 1% to < 5%, and severe when factor levels are < 1%. Joint bleeds are the most frequent bleeding experienced by people with hemophilia of all severities (70-80%) which can lead to deformity, arthropathy, and irreversible joint damage leading to decreased mobility. Given the complexities of diagnosis and treatment of hemophilia A and B, supervision of treatment by a hematologist is required.
- IV. The World Federation of Hemophilia (WFH) guidelines recommend use of agents for both bleeding prophylaxis and control of acute breakthrough bleeds. Therapy recommendations are not sequential, but rather cite the need for individualized care considering a patient's bleeding phenotype, joint status, pharmacokinetic profile, and preference. Medications include factor replacement with clotting factor concentrates (CFCs) (i.e., standard half-life (SHLs) for FVIII for hemophilia A and FIX for hemophilia B), long-acting CFCs (i.e., extended half-life (EHLs)), non-factor, and gene therapies. The frequency of injections varies but overall injection burden is high. Guidelines have not been updated to include marstacimab (Hypavzi).
- V. There are varying severities of hemophilia A and B depending on the level of factor produced by the patient, these are divided into the following per the International Society on Thrombosis and Hemostasis (ISTH):
 - Severe: <1% factor activity (<0.01 IU/mL)
 - Moderate: Factor activity level $\geq 1\%$ of normal and $\leq 5\%$ of normal (≥ 0.01 and ≤ 0.05 IU/mL)
 - Mild: Factor activity level >5% of normal and < 40% of normal (> 0.05 and < 0.40 IU/mL)
- VI. There is a lack of strong scientific evidence from randomized controlled trials supporting the efficacy and safety of multiple agents for routine prophylaxis used in combination. Therefore, use of marstacimab (Hypavzi) in combination with other agents for routine prophylaxis [i.e., factor replacement (Advate, Eloctate, BeneFIX, etc.), bypassing agent (NovoSeven, FEIBA, Sevenfact), non-factor replacement therapy (emicizumab-kxwh (Hemlibra)), etc.] is not allowable per policy. There is a lack of head-to-head trials showing superior safety or efficacy comparing marstacimab (Hypavzi) to other prophylactic agents for the treatment of hemophilia A or B. Given the known safety, established efficacy, and cost-effectiveness of these therapies, prior prophylaxis with factor VIII and emicizumab-kxwh (Hemlibra), or factor IX

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remains the preferred specialty agents by this plan due to efficacy, safety, and cost. Marstacimab (Hypmavzi) is specifically more costly than other agents, despite not having any evidence of improved clinical efficacy or safety.

- VII. Marstacimab (Hypmavzi) was studied in the BASIS trial, a Phase 3, one-way, crossover, open-label, study in adolescent and adult participants with severe hemophilia A (coagulation FVIII activity < 1%) or moderate to severe hemophilia B (coagulation FIX activity ≤ 2%). Patients in the routine FVIII/FIX prophylaxis (RP) group were required to have demonstrated at least 80% compliance while participants in the on-demand (OD) treatment group were required to have ≥6 acute bleeding episodes requiring factor infusion during the six months prior to enrollment. Those using a bypassing agent, non-coagulation non-factor replacement therapy, or any previous gene therapies were excluded. The primary outcome was reduction in the annualized bleeding rate (ABR) for treated patients compared to their own current standard treatment versus a 12-month active phase of participants receiving prophylaxis treatment with marstacimab (Hypmavzi). Among the 116 patients treated with marstacimab (Hypmavzi), the mean age was 32 years (range 13 to 66), 91 (78%) with hemophilia A and 25 (22%) with hemophilia B. All patients in the OD cohort had one or more target joints at study entry and 36% had three or more target joints at study entry. Whereas in the RP cohort, 57% of the patients had one or more target joints at study entry and 16% had three or more target joints at study entry.
- VIII. The results of the BASIS clinical trial showed that marstacimab (Hypmavzi) prophylaxis demonstrated statistical superiority over OD treatment and noninferiority over RP treatment with factor-based therapies, as measured by the ABR of bleed events. It is unknown how marstacimab (Hypmavzi) compared to prophylaxis with bypassing or subcutaneous non-factor therapies [e.g., (emicizumab-kxwh (Hemlibra))] as participants treated with these agents were excluded under the protocol. The bias of an open-label treatment design may be mitigated as bleed events are objective and each participant went through the observation phase with their own standard therapy before crossing over to marstacimab (Hypmavzi). While not statistically evaluated in the hierarchical testing procedure, marstacimab (Hypmavzi) numerically improved Hemophilia Joint Health Scores; however, the minimal clinically important difference was not achieved. Long term safety and efficacy is still relatively unknown and will be realized in the real-world setting. Therefore, the quality of evidence is considered moderate.
- IX. Marstacimab (Hypmavzi) was not directly compared with to prophylaxis with bypassing or subcutaneous non-factor therapies for the treatment of hemophilia A or B. Balancing long-term safety data, efficacy, and costs of alternative therapies compared to marstacimab (Hypmavzi), treatment with prior prophylactic factor therapies and emicizumab-kxwh (Hemlibra), when applicable, is required.
- X. For individuals who have had more than one bleeding episode (e.g., two or more bleeds into a target joint, evidence of joint disease by physical exam or radiography), prophylaxis may be appropriate to prevent further morbidity, regardless of factor activity level. Use of on demand therapy in those with mild-to-moderate disease with less than two instances of spontaneous bleeding is considered clinically appropriate for the management of hemophilia.
- XI. Dose escalation from a starting dose of 150 mg to 300 mg of marstacimab (Hypmavzi) once weekly was permitted in the clinical trial setting and is an FDA approved dosing regimen. Those participants weighing ≥50 kg and experiencing two or more breakthrough bleeds after undergoing six months of treatment were eligible for dose escalation. While use of prophylactic therapies reduces the number of bleed events patients with hemophilia will still experience bleeds. Therefore, dose escalation should be considered for those most at risk of bleed events.

Investigational or Not Medically Necessary Uses

- I. Marstacimab (Hypmavzi) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Marstacimab (Hypmavzi) used in combination with other agents for routine prophylaxis [i.e., factor replacement (Advate, Eloctate, BeneFIX, etc.), bypassing agent (NovoSeven, FEIBA, Sevenfact), non-factor replacement therapy (emicizumab-kxwh (Hemlibra)), etc.]
 - i. Use of dual therapies for routine prophylaxis have not been evaluated for safety and efficacy.
 - B. Pediatric patients <12 years of age with hemophilia A or B
 - i. Clinical trial data is currently limited to adult and adolescent patients 12 years of age and older. BASIS KIDS, an open-label study investigating the safety and efficacy of marstacimab in children 1 to <18 years of age with severe hemophilia A or moderately severe to severe hemophilia B with or without inhibitors is still ongoing.
 - C. Hemophilia A & B with inhibitors
 - i. The published efficacy data from the BASIS trial only consisted of the without inhibitor cohort. Clinical trials are still ongoing to determine the safety and efficacy of marstacimab (Hypmavzi) in those without inhibitors. The inhibitor cohort of the BASIS trial is ongoing, with results expected in the third quarter of 2025.
 - D. Mild-to-moderate hemophilia A (Factor activity level $\geq 1\%$ of normal and < 40% of normal (≥ 0.01 and < 0.40 IU/mL) and Mild hemophilia B (Factor activity level >5% of normal and < 40% of normal (> 0.05 and < 0.40 IU/mL)
 - i. Data from the BASIS clinical trial program is limited to those with severe hemophilia A (defined as factor VIII level of <1%) or moderate to severe hemophilia B (defined as factor IX level of less than or equal to 2% in clinical trials). Use for the treatment of mild to moderate disease has not been evaluated in clinical trials.

References

1. Hypmavzi. Package Insert. Pfizer Inc; October 2024.
2. Matino D, Acharya S, Palladino A, et al. Efficacy and safety of the anti-tissue factor pathway inhibitor marstacimab in participants with severe hemophilia without inhibitors: results from the phase 3 BASIS trial. *Blood*. 2023;142 (suppl 1):abstr 285. <https://doi.org/10.1182/blood-2023-181263>
3. Srivastava A, Santagostino E, Dougall A, et al. WFH Guidelines for the Management of Hemophilia, 3rd edition. *Haemophilia*. 2020; 26(Suppl 6): 1-158.
4. Hypmavzi product dossier. Pfizer. October 17, 2024.

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
emicizumab-kxwh (Hemlibra®) – Hemophilia A	Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients ages newborn and older with hemophilia A with or without factor VIII inhibitors

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Standard Half-life Factor VIII Products – Hemophilia A	On-demand Treatment
	Routine Prophylaxis
	Perioperative Management
Standard Half-life Factor IX Products – Hemophilia B	Control and prevention of bleeding episodes
	Perioperative management
	Routine Prophylaxis
Bypassing Agents – Hemophilia A & B	Control and prevention of bleeding – Hemophilia A or B with inhibitors
	Routine prophylaxis – Hemophilia A or B with inhibitors
	Perioperative management – Hemophilia A or B with inhibitors
	Control and prevention of bleeding episodes – Acquired hemophilia
	Control and prevention of bleeding episodes – Factor VII deficiency
	Control and prevention of bleeding episodes – Glanzmann’s Thrombasthenia
	Perioperative management – acquired hemophilia
	Perioperative management – factor VII deficiency
	Perioperative management – Glanzmann’s Thrombasthenia
Extended Half-life Factor VIII Products – Hemophilia A	On-demand Treatment
	Routine Prophylaxis
	Perioperative Management
Extended Half-life Factor IX Products – Hemophilia B	On-demand Treatment
	Routine Prophylaxis
	Perioperative Management

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	02/2025

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP253

Description

Mavacamten (Camzyos) is an orally administered selective allosteric inhibitor of cardiac myosin ATPase.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
mavacamten (Camzyos)	2.5 mg capsule	Symptomatic NYHA Class II-III obstructive hypertrophic cardiomyopathy (oHCM)	30 capsules/30 days
	5 mg capsule		
	10 mg capsule		
	15 mg capsule		

Initial Evaluation

- I. **Mavacamten (Camzyos)** 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 who practices at or consults with a Center of Excellence for hypertrophic cardiomyopathy; **AND**
 - C. A diagnosis of **symptomatic NYHA Class II-III obstructive hypertrophic cardiomyopathy (oHCM)** when the following are met:
 1. Provider attestation the member has undergone a comprehensive cardiac workup to diagnose hypertrophic cardiomyopathy (e.g., physical exam, ECG, ECHO, CMR, etc.); **AND**
 2. Provider attestation that baseline obstruction by left ventricular outflow tract (LVOT) gradient is 50 mm Hg or greater; **AND**
 3. Provider attestation that member has NYHA Class II-III symptoms of heart failure, including but not limited to, fatigue, dyspnea, chest pain, palpitations, and syncope; **AND**
 - D. Treatment with one of the following regimens has been ineffective, contraindicated, or not tolerated:
 1. Beta-blocker (e.g., metoprolol, carvedilol, bisoprolol, etc.) in combination with non-dihydropyridine calcium channel blocker (e.g., verapamil, diltiazem); **OR**
 2. Disopyramide in combination with beta-blocker and/or non-dihydropyridine calcium channel blocker.

- II. Mavacamten (Camzyos) is considered investigational when used for all other conditions, including but not limited to:
 - A. Asymptomatic oHCM
 - B. Non-obstructive hypertrophic cardiomyopathy
 - C. Dilated, arrhythmogenic or restrictive cardiomyopathy
 - D. Cardiac amyloidosis or amyloid cardiomyopathy
 - E. Fabry 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 [e.g., improved fatigue, dyspnea, chest pain, palpitations, and/or syncope, improved exercise capacity, reduction in LVOT gradient, etc.].

Supporting Evidence

- I. Length of authorization for initial approval is six months as clinical benefits of mavacamten were realized in clinical trials as early as 18 weeks and were evaluated at 30 weeks of therapy. Treatment response is expected to be realized at six months duration.
- II. Hypertrophic cardiomyopathy (HCM) is a genetic disease of the sarcomeres in cardiac muscle that causes structural and hemodynamic abnormalities of the heart. The disease typically manifests as left ventricular hypertrophy which can lead to LVOT obstruction, diastolic or systolic dysfunction, myocardial ischemia, and mitral regurgitation. Diagnosis of HCM is made by a cardiologist through a comprehensive cardiac workup, including, but not limited to, an electrocardiogram (ECG) and echocardiograph (ECHO) or cardiac magnetic resonance imaging (CMR). The LVOT gradient, an indicator of obstruction, is measured by ECHO, CMR, or invasive assessment through cardiac catheterization; a value of 30 mm Hg or greater indicates obstruction, while resting or provoked gradients at or greater than 50 mm Hg represent a threshold for septal reduction therapy in patients who have drug-refractory symptoms. Symptoms of HCM include fatigue, dyspnea, chest pain, palpitations, and syncope. Several disease-related complications may also occur, including atrial fibrillation, ventricular arrhythmia, progressive heart failure, and embolic stroke. Given the specialized monitoring this condition entails, a specialist prescriber who practices at or consults with a Center of Excellence designed to care for HCM patients is required.
- III. Current guidelines (2014 European Society of Cardiology, 2020 American Heart Association/American College of Cardiology) provide treatment recommendations for HCM based on presence of heart failure symptoms, obstruction, and disease-related comorbidities. Treatment is not recommended for asymptomatic patients. In patients with symptoms of heart

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failure and obstruction (oHCM), BB (metoprolol, carvedilol, bisoprolol) or non-dihydropyridine calcium CCB (verapamil, diltiazem), monotherapy is recommended. Second-line therapies include combination BB plus CCB, or addition of antiarrhythmic disopyramide to BB and/or CCB. If symptoms persist despite maximal pharmacologic therapy, septal reduction therapy (SRT) is indicated in the form of surgical myectomy or alcohol ablation; SRT may also be considered as an alternative to escalation of pharmacologic therapy if symptoms are severe. In patients with symptomatic HCM without obstruction, treatment includes BB, CCB, ACE-inhibitors and angiotensin-receptor blockers (ARB), and diuretics. Treatment of comorbid atrial fibrillation, ventricular arrhythmia, and thromboembolic risk includes rate and rhythm control strategies and anticoagulants; cardioversion, ICD placement, catheter ablation, and heart transplant may also be used if symptoms are severe or drug-refractory.

- Treatment Summary: In patients refractory to single-agent BB or CCB, escalation to combination BB plus CCB or addition of disopyramide to one or both of these therapies are viable treatment options. Given the known efficacy, established safety profile, and cost effectiveness of these medications, at least one dual therapy regimen is required prior to mavacamten.

- IV. The FDA-approval of mavacamten (Camzyos) for oHCM was based on the results of one 30-week international, randomized, double-blind, placebo-controlled Phase 3 study: EXPLORER-HCM. A total of 251 adults with symptomatic oHCM were enrolled, as defined by unexplained left ventricular hypertrophy and at least one peak LVOT gradient 50 mm Hg or greater at rest, after Valsalva, or post-exercise, NYHA class II or III symptoms, left ventricular ejection fraction (LVEF) 55% or greater, and LVOT at screening of 30 mm Hg or greater. Population characteristics were as follows: 73% NYHA class II, 75% on BB, 16.5% on CCB, 14% with atrial fibrillation, 7.5% previous septal reduction procedure, average LVEF 74%. Mavacamten doses were titrated as guided by ECHO to achieve a target left ventricular outflow tract (LVOT) gradient of less than 30 mm Hg and drug plasma concentration of 350-700 ng/mL. The primary endpoint was the number of patients who achieved a clinical response composite at week 30, as defined by a ≥ 1.5 mL/kg/min increase in peak oxygen consumption (pVO_2) and ≥ 1 NYHA class improvement or ≥ 3 mL/kg/min increase in pVO_2 and no worsening of NYHA class; this was met in 37% of the mavacamten group compared to 17% of the placebo group, with a clinically meaningful and statistically significant difference relative to placebo. Key secondary endpoints included change from baseline to week 30 in post-exercise left ventricular outflow tract (LVOT) gradient, pVO_2 , patient reported outcome measure of symptom reduction and physical function (Kansas City Cardiomyopathy Questionnaire-Clinical Summary Score, KCCQ-CSS) and number of patients with at least one NYHA class improvement; all secondary endpoints were met with a clinically meaningful difference relative to placebo. The most common adverse events were nasopharyngitis, dizziness, headache, and dyspnea.
- V. Consistent with the mechanism of action, mavacamten (Camzyos) reduces LVEF and can cause systolic dysfunction, which can also be exacerbated when taken with certain cytochrome P450 inhibitors/inducers. As a result, mavacamten carries a warning for heart failure and is only available through a restricted REMS program called Camzyos REMS. ECHO assessments are required before and during treatment with mavacamten (Camzyos).

Investigational or Not Medically Necessary Uses

- I. Mavacamten (Camzyos) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Asymptomatic oHCM
 - B. Non-obstructive hypertrophic cardiomyopathy
 - C. Dilated, arrhythmogenic or restrictive cardiomyopathy
 - D. Cardiac amyloidosis or amyloid cardiomyopathy
 - E. Fabry disease

References

1. Olivetto I, Oreziak A, Barriaes-Villa R, et al. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2020;396(10253):759-769.
2. Ho CY, Olivetto I, Jacoby D, et al. Study design and rationale of EXPLORER-HCM: evaluation of mavacamten in adults with symptomatic obstructive hypertrophic cardiomyopathy. *Circ: Heart Failure*. 2020;13(6).
3. Rader F, Choudhury L, Saberi S, et al. Long-term safety of Mavacamten in patients with obstructive hypertrophic cardiomyopathy: interim results of the MAVA-long term extension (LTE) study. *J Am Coll Cardiol*. 2021;77(18):532.
4. Institute for Clinical and Economic Review. Mavacamten for Hypertrophic Cardiomyopathy: Effectiveness and Value. October 7, 2021. Accessed November 9, 2021. https://icer.org/wp-content/uploads/2021/04/ICER_HCM_Revised_Report_100721.pdf
5. Ommen SR, Mital S, Burke MA, et al. 2020 AHA/ACC guideline for the diagnosis and treatment of patients with hypertrophic cardiomyopathy: executive summary: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *J Am Coll Cardiol*. 2020;76(25):3022-3055.
6. 2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy: the task force for the diagnosis and management of hypertrophic cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J*. 2014;35(39):2733-2779.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created.	02/2022

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP307

Description

Mavorixafor (Xolremdi) is an oral selective CXCR4 chemokine receptor 4 (CXCR4) antagonist.

Length of Authorization

- Initial: 6 months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
mavorixafor (Xolremdi)	Warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome	100 mg tablets	<u>Weight > 50 kg:</u> 120 tablets/30 days <u>Weight ≤ 50 kg:</u> 60 tablets/20 days

Initial Evaluation

- I. **Mavorixafor (Xolremdi)** may be considered medically necessary when the following criteria are met:
 - A. Member is 12 years of age or older; **AND**
 - B. Documentation of member's weight is provided (kg); **AND**
 - C. Medication is prescribed by, or in consultation with, a hematologist or immunology specialist; **AND**
 - D. Medication will not be used in combination with another CXCR4 antagonist (e.g., plerixafor (Mozobil), motixafortide (Aphexda)); **AND**
 - E. Member has a diagnosis of **warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome** when the following are met:
 1. Documentation of genotype-confirmed mutation of *CXCR4* consistent with warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) phenotype; **AND**
 2. Documentation of severe symptoms and complications associated with warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome (e.g., history of recurrent infections, chronic neutropenia, history of lymphopenia, history of hypogammaglobulinemia, detected myelokathexis, refractory or recalcitrant warts, etc.); **AND**
 3. Documentation of absolute neutrophil count (ANC) < 500 cells/μL that is not related to medication, chemotherapy, or secondary to viral infections; **AND**
 - F. Treatment with a granulocyte-colony stimulating factor (G-CSF) (e.g., filgrastim-sndz (Zarxio), pegfilgrastim-apgf (Nyvepria), pegfilgrastim-jmdb (Fulphila) etc.) has been ineffective, contraindicated, or not tolerated.

- II. Mavorixafor (Xolremdi) is considered investigational when used for all other conditions, including but not limited to:
 - A. Chronic neutropenia (congenital, acquired primary autoimmune, and idiopathic)
 - B. Melanoma
 - C. Renal Cell Carcinoma
 - D. Waldenstrom macroglobulinemia
 - E. Alzheimer's and Parkinson's diseases
 - F. HIV-1

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 weight is provided (kg); **AND**
- IV. Medication will not be used in combination with another CXCR4 antagonist (e.g., plerixafor (Mozobil), motixafortide (Aphexda)); **AND**
- V. Member has exhibited sustained improvement in absolute neutrophil count (ANC) and/or absolute lymphocyte count (ALC); **OR**
 - A. Member has exhibited improvement or stability of disease symptoms [e.g., reduced incidence or severity of infections from baseline, reduction from baseline or severity of warts, etc.]

Supporting Evidence

- I. 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, human papillomavirus (HPV) infections, and cancer. 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.
- II. Mavorixafor (Xolremdi) is a selective CXC chemokine receptor 4 (CXCR4) antagonist and the first FDA-approved treatment specifically indicated in patients with WHIM syndrome. Historically, treatment targeted symptoms of WHIM and included the use of granulocyte-colony stimulating factor (G-CSF), Immunoglobulin (Ig), and antibiotics requiring coordination between specialists, such as hematologists and immunologists. 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, etc.
- III. 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 mavorixafor (Xolremdi). The prescriber must confirm

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that the member has a specific diagnosis of WHIM syndrome based on confirmation of the *CXCR4* gene, documentation of personal history of severe symptoms and complications associated with WHIM syndrome, and neutropenia based on absolute neutrophil count (ANC) count.

- IV. The absolute neutrophil count (ANC) is the absolute number of segmented neutrophils (also called polys or segs) and band forms ($[\text{WBC count per microliter}] \times [\text{percentage of neutrophils} + \text{band forms}]$). An ANC below 1000 cells/ μL is defined as neutropenia and associated with increased risk of infection.
- V. Approval for mavorixafor (Xolremdi) was based on results of the Phase 3, randomized, double-blind, placebo-controlled, 52-week multicenter study (4WHIM) that evaluated the efficacy and safety of mavorixafor (Xolremdi) in 31 participants. Patients 12 years of age and older were randomized in a 1:1 ratio to receive mavorixafor (N=14) based on weight (>50 kg, 400mg; ≤ 50 kg, 200mg) or placebo (N=17) orally once daily. Patients all had a genotype-confirmed variant of *CXCR4* consistent with WHIM syndrome, confirmed absolute neutrophil count (ANC) ≤ 400 cells/ μL , and were eligible to continue on IVIG therapy. The primary endpoint was defined as number of hours above ANC threshold (500 cells/ μL) over a 24-hour period, assessed every 3 months for 52 weeks. Mavorixafor (Xolremdi) achieved a mean time of 15.04 hours versus placebo at 2.75 hours ($p < 0.0001$). The key secondary endpoint of number of hours above absolute lymphocyte count (ALC) of ≥ 1000 cells/ μL over a 24-hour period was also met with mavorixafor (Xolremdi) having a mean time of 15.80 hours versus placebo at 4.55, ($p < 0.0001$).
- VI. Mavorixafor (Xolremdi) showed positive trends in secondary endpoints demonstrating less severe and fewer number of infections, a statistically significant reduction ($\sim 60\%$) in annualized infection rate versus placebo ($p < 0.01$), 71% less time with infection, and lower rate of antibiotic usage compared with placebo. The use of mavorixafor (Xolremdi) on warts has uncertain benefit as there was no difference in total wart change scores between treatment arms; however, minor reduction in wart score occurred in both mavorixafor and placebo groups. Additionally, no new warts were observed in mavorixafor (Xolremdi) group for participants without warts at baseline.
- VII. The safety was established by all patients receiving at least one dose of mavorixafor (Xolremdi). Seven (50%) of patients in mavorixafor (Xolremdi) compared to 3 (18%) patients in placebo experienced treatment-related adverse events (TEAEs). The most common adverse reactions ($\geq 10\%$ and at a frequency higher than placebo) in the mavorixafor (Xolremdi) arm were thrombocytopenia, pityriasis, rash, rhinitis, epistaxis, vomiting, and dizziness. The placebo arm had increased infections/infestations and respiratory disorders. Serious adverse reactions of thrombocytopenia occurred in 3 of the 14 patients who received mavorixafor (Xolremdi), two of which occurred in the setting of infection or febrile neutropenia. There were no TEAEs that led to discontinuations or death. Mavorixafor (Xolremdi) carries an embryo-fetal toxicity, QTc interval prolongation warning, and is contraindicated with drugs highly dependent on CYP2D6 for clearance.
- VIII. 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

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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.

- IX. While G-CSF's have not been directly compared to mavorixafor (Xolremdi), they have been studied against another CXCR4 inhibitor, plerixafor, in WHIM syndrome (NCT02231879). In a Phase 3 crossover trial of plerixafor versus G-CSF (N = 19), no differences between the G-CSF and plerixafor arms were found for any infection outcome measures. In exploratory endpoints, plerixafor was noninferior 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). There were no significant differences in drug preference, quality of life, or the incidence of drug failure or serious adverse events.
- X. Mavorixafor (Xolremdi) has not been studied in combination with other CXCR4 antagonists such as plerixafor (Mozobil) or motixafortide (Aphexda). The combination use of these agents for safety and efficacy remains unknown at this time.
- XI. There is moderate confidence that the medication provides a clinically objective and meaningful benefit as the medication provides a similar overall treatment profile balancing safety and efficacy relative to comparable treatment options, which include G-CSFs and other CXCR4 antagonists. Results from the 4WHIM trial demonstrate the ability for mavorixafor (Xolremdi) to raise and maintain ANC and ALC levels over a period of time. Absolute neutrophil count (ANC) and ALC values are used to predict the risk of serious bacterial infections in patients with neutropenia and lymphopenia. Mavorixafor (Xolremdi) provides a statistically significant difference in increasing the number of circulating mature neutrophils and lymphocytes in patients with WHIM syndrome. Furthermore, mavorixafor (Xolremdi) showed positive trends in secondary endpoints compared with placebo. The full extent of efficacy and utility of mavorixafor (Xolremdi) will be realized in the real-world setting. An ongoing extension study is evaluating the long-term safety and efficacy of mavorixafor (Xolremdi).

Investigational or Not Medically Necessary Uses

- I. Mavorixafor (Xolremdi) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Chronic neutropenic disorders (congenital, acquired primary autoimmune, and idiopathic)
 - i. Phase 3, 4WARD trial (NCT06056297) aims to evaluate the efficacy, safety, and tolerability of oral once-daily mavorixafor (Xolremdi) with or without granulocyte colony-stimulating factor (G-CSF) in participants with congenital or acquired primary autoimmune and idiopathic chronic neutropenia. The trial started enrolling 2024 and results are expected end of 2025. The current standard of care for treating severe chronic neutropenia is G-CSF therapy.
 - B. Melanoma
 - C. Renal Cell Carcinoma
 - D. Waldenstrom macroglobulinemia
 - E. Alzheimer's and Parkinson's diseases
 - F. HIV-1

Appendix

- I. Mavorixafor (Xolremdi) dosing:
 - a. Weight >50 kg: 400 mg orally once daily
 - b. Weight ≤50 kg: 300 mg orally once daily
- I. Mavorixafor (Xolremdi) is contraindicated with drugs that are highly dependent on CYP2D6 for clearance.
- II. Examples of G-CSF therapies:

Short-acting G-CSF	Long-acting G-CSF
filgrastim-sndz (Zarxio)*	pegfilgrastim-apgf (Nyvepria)*
filgrastim (Neupogen)	pegfilgrastim-jmdb (Fulphila)*
filgrastim-aafi (Nivestym)	Pegfilgrastim (Neulasta, Neulasta Onpro)
tbo-filgrastim (Granix)	pegfilgrastim-cbqv (Udenyca, Udenyca ON-BODY)
filgrastim-ayow (Releuko)	pegfilgrastim-bmez (Ziextenzo)
sargramostim (Leukine)	Pegfilgrastim (Neulasta)
	pegfilgrastim-pbbk (Fylmetra)
	pegfilgrastim-fpgk (Stimufend)

*as of July 2023, is a preferred G-CSF and does not require a prior authorization unless requesting above the plan's set quantity limits

References

1. Xolremdi. Package insert. X4 Pharmaceuticals Inc; April 2024.
2. whatifitwhim. Understanding whim syndrome: diagnosis, management, and resources. Accessed July 10, 2024. <https://www.whatifitwhim.com/diagnosis-and-management/>
3. Badolato R, Alsina L, Azar A, et al. Phase 3 randomized trial of mavorixafor, CXCR4 antagonist, in WHIM syndrome. *Blood*. 2024; <https://doi.org/10.1182/blood.2023022658>
4. Badolato R, et al; WHIM Research Group. How I treat warts, hypogammaglobulinemia, infections, and myelokathexis syndrome. *Blood*. 2017;130(23):2491-2498. doi:10.1182/blood-2017-02-708552
5. National Organization for Rare Diseases (NORD). WHIM Syndrome. January 16, 2024. Accessed May 23, 2024. <https://rarediseases.org/rare-diseases/whim-syndrome>
6. Dale DC, Firkin F, Bolyard AA, et al. Results of a phase 2 trial of an oral CXCR4 antagonist, mavorixafor, for treatment of WHIM syndrome [published correction appears in *Blood*. 2023 Jun 29;141(26):3232]. *Blood*. 2020;136(26):2994-3003. doi:10.1182/blood.2020007197
7. McDermott DH, Velez D, Cho E, et al. A phase III randomized crossover trial of plerixafor versus G-CSF for treatment of WHIM syndrome. *J Clin Invest*. 2023;133(19):e164918. Published 2023 Oct 2. doi:10.1172/JCI164918
8. Sermer D, Sarosiek S, Branagan AR, Treon SP, Castillo JJ. SOHO State of the Art Updates and Next Questions: Targeted therapies and emerging novel treatment approaches for Waldenström Macroglobulinemia. *Clin Lymphoma Myeloma Leuk*. 2022;22(8):547-556. doi:10.1016/j.clml.2022.02.005
9. Tripathi R, Kumar P. Preliminary study to identify CXCR4 inhibitors as potential therapeutic agents for Alzheimer's and Parkinson's diseases. *Integr Biol (Camb)*. 2023;15:zyad012. doi:10.1093/intbio/zyad012

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
Short-acting Granulocyte-colony stimulating factor (CSF)	Severe chronic neutropenia
	WHIM syndrome
Long-acting Granulocyte Colony Stimulating Factor (G-CSF)	WHIM syndrome

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Policy Implementation/Update

Action and Summary of Changes	Date
Policy created	08/2024

Policy Type: PA

Pharmacy Coverage Policy: UMP232

Description

Mecamylamine (Vecamyl) is an orally administered sympathetic ganglionic blocker, which blocks cholinergic stimuli at nicotinic receptors leading to blood vessels dilation and reduction in blood pressure.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
Mecamylamine (Vecamyl)	2.5 mg tablet	Moderately severe to severe hypertension	300 tablets/30 days
		Uncomplicated malignant hypertension	

Initial Evaluation

- I. Mecamylamine (Vecamyl) 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 **Moderately severe to severe hypertension OR Uncomplicated malignant hypertension** when the following are met:
 1. Treatment with at least one agent from FIVE of the following classes of antihypertensive agents has been ineffective or not tolerated (Note, if a class of agents is contraindicated, a trial and failure of at least five agents or combinations thereof from the remaining groups is required):
 - i. Thiazide diuretics (e.g. hydrochlorothiazide)
 - ii. Angiotensin-converting enzyme inhibitors (e.g. lisinopril, captopril, benazepril)
 - iii. Angiotensin II receptor antagonists (e.g. losartan, valsartan)
 - iv. Beta blockers (e.g. metoprolol)
 - v. Calcium channel blockers (e.g. amlodipine, diltiazem)
 - vi. Direct renin inhibitors (e.g. aliskiren)
 - vii. Other (e.g. clonidine, hydralazine, doxazosin) **AND**

2. Treatment with at least one parenteral antihypertensive agent (e.g. IV nitroprusside, nicardipine, clevidipine, labetalol) has been ineffective, contraindicated, or not tolerated.
- II. Mecamylamine (Vecamyl) is considered investigational when used for all other conditions, including but not limited to:
 - A. Major depressive disorder (MDD)
 - B. Gilles de la Tourette's syndrome
 - C. Hyperreflexia
 - D. Nicotine dependence

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 blood pressure].

Supporting Evidence

- I. Mecamylamine (Vecamyl) is a nicotinic parasympathetic ganglionic blocker, which prevents stimulation of postsynaptic receptors by acetylcholine released from presynaptic nerve endings. The hypotensive effect of mecamylamine (Vecamyl) is attributed to reduction in sympathetic tone, vasodilation, and reduced cardiac output. It is considered a nonselective antagonist that easily passes through the blood-brain barrier, and thus, having the potential to affect nicotinic acetylcholine receptors in the central nervous system.
- II. Mecamylamine (Vecamyl) is FDA approved for use in patients 18 years of age and older. Efficacy and safety of this drug are not established in the pediatric population.
- III. Mecamylamine (Vecamyl) should be given with great discretion, if at all, when renal insufficiency is manifested by a rising or elevated BUN. The drug is contraindicated in uremia. Patients receiving antibiotics and sulfonamides should generally not be treated with ganglion blockers. Other contraindications are glaucoma, organic pyloric stenosis, or hypersensitivity to the product.
- IV. The package insert for mecamylamine (Vecamyl) does not include any clinical trials as it was approved using an abbreviated new drug application (ANDA) of the innovator product, mecamylamine (Inversine). Approved on March 1, 1956, Inversine was available prior to the 1962 amendments to the Federal Food, Drug, and Cosmetic Act, which led to inclusion of Inversine as an approved DESI drug; however, the distribution of Inversine was discontinued in 2009.

- V. An observational clinical study (N=17) in 1957 examined the effects of mecamylamine monotherapy for blood pressure reduction from baseline (>150/100 mm Hg). Each patient was initiated on mecamylamine 2.5mg twice daily before undergoing a set dose titration. Treatment response was defined as a decrease in mean blood pressure by at least 20 mm Hg or a reduction of blood pressure to the normotensive level (defined by the investigators as less than 150/100 mm Hg). Response rate to mecamylamine was reported to be 52% at average 34 mg/day dose, while the other half of subject population (non-responders) had no blood pressure reductions despite doubling the average dose.
- VI. Mecamylamine (Vecamyl) is not an acceptable alternative agent to consider for supplemental use after first-line antihypertensive agents have failed to provide adequate response. More predictably effective agents with proven effects on morbidity and mortality and with safer side effect profiles have replaced mecamylamine for use in both essential and accelerated hypertension.
- VII. It should be noted that parenteral antihypertensives (e.g. IV nitroprusside, nicardipine, clevidipine, labetalol etc.) are most often used in the initial treatment of malignant hypertension due to their faster onset of action. Trial of a parenteral antihypertensive agent is warranted before consideration of mecamylamine (Vecamyl) as the next therapeutic agent.
- VIII. The Clinical Practice Guidelines from the American College of Cardiology/American Heart Association Task Force (2017) do not include ganglionic blockers (e.g. mecamylamine (Vecamyl)) as a recommended primary or secondary treatment option. The Evidence-Based Guideline for the Management of High Blood Pressure in Adults from the panel members of the eighth joint national committee (2014) advise selection among four specific medication classes (thiazide type diuretics, calcium channel blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers) as initial treatment and inclusion of other classes (e.g. beta blockers, direct renin inhibitors, alpha1 blockers, centrally acting drugs and direct vasodilator) as secondary choices in treatment.

Investigational or Not Medically Necessary Uses

- I. Major depressive disorder (MDD)
 - A. The principal focus of research on mecamylamine largely involves its potent blockade of nicotinic receptors in central nervous system at doses that do not have a significant effect on parasympathetic function (2.5-10 mg/day). Recently mecamylamine was studied via two short-term, phase III clinical trials, as an add-on treatment to existing antidepressant agents. These trials did not show significant difference in treatment groups compared to a placebo.
- II. Gilles de la Tourette's syndrome and Hyperreflexia
 - A. Use of mecamylamine for the treatment of Gilles de la Tourette's syndrome and hyperreflexia has been studied in retrospective case studies and the quality of evidence in these settings is considered low.
- III. Nicotine dependence
 - A. A randomized, double-blind, placebo controlled clinical trial (N=48) assessed efficacy of mecamylamine in combination with transdermal nicotine patches as compared to placebo in combination with nicotine patch. Although this study reported greater abstinence rates

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in treatment group at week 7 (50% versus 16%), the trial was not adequately powered to analyze effect size and the primary outcome assessment was based on patient self-reporting. Additionally, all subjects received transdermal nicotine, which confounded the outcomes assessment. Mecamylamine has not been FDA-approved in this setting.

References

1. Vecamyl [Prescribing Information]. Fort Collins, CO: Manchester Pharmaceuticals; July 2015.
2. Shytle RD, Penny, E, et. al. Mecamylamine (Inversine): an old antihypertensive with new research directions. Journal of Human Hypertension. 2002; (16): 453-457.
3. The Death of TC-5214. Kefauver-Harris Amendments Revolutionized Drug Development. Updated on October 10, 2012. Available at <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm322856>.
4. Moyer, John; Heider, Charles; Dennis, Edward. Mecamylamine (Inversine) in the treatment of hypertension. JAMA. 1957;164(17):1879-1886.
5. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. JACC,. 2018; 71, e127-248.

Policy Implementation/Update:

Action and Summary of Changes	Date
Transition of old criteria document to the policy format; added requirement of drug being prescribed by a specialist; removed criteria for validation of contraindications before treatment start; added E/I uses; added supporting evidence	05/2021
Criteria created	09/2013

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP133

Description

Mecasermin (Increlex) is an injection that is indicated for the treatment of growth failure in children with severe primary insulin-like growth factor (IGF-1) deficiency or with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
mecasermin (Increlex)	40 mg/4 mL multiple dose vial	Severe primary insulin-like growth factor (IGF-1) deficiency; Growth hormone (GH) gene deletion with neutralizing antibodies to GH	7.2 mg/kg/30 days

Initial Evaluation

- I. Mecasermin (Increlex) may be considered medically necessary when the following criteria below are met:
 - A. Member is a between 2-18 years of age; **AND**
 - B. Medication is prescribed by, or in consultation with, a pediatric endocrinologist or a pediatric nephrologist; **AND**
 - C. Member has evidence of non-closure of the epiphyseal plate confirmed by radiograph; **AND**
 - D. A diagnosis of one of the following:
 1. **Severe primary insulin-like growth factor (IGF-1) deficiency**
 - i. Member meets ALL of the following:
 - a. Height standard deviation score ≤ -3.0 ; **AND**
 - b. Basal IGF-1 standard deviation score ≤ -3.0 ; **AND**
 - c. Normal or elevated growth hormone (GH) level, [serum growth hormone level of ≥ 10 ngm/mL to at least two stimuli (insulin, levodopa, arginine, clonidine, or glucagon)]; **OR**
 2. **Growth hormone (GH) gene deletion**
 - i. Member has developed neutralizing antibodies to GH; **AND**
 - ii. Member has normal thyroid function (TSH in the range of 0.5-6 uIU/mL); **AND**

- iii. Member is not malnourished (BMI < 18 kg/m²); **AND**
 - iv. Member does not have active or suspected neoplasia (e.g. cancer)
- II. Mecasermin (Increlex) is considered investigational when used for all other conditions, including but not limited to:
 - A. Secondary forms of IGF-1 deficiency such as:
 - 1. GH deficiency
 - 2. Malnutrition
 - 3. Hypothyroidism
 - 4. Chronic treatment with pharmacologic doses of anti-inflammatory steroids

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through the health plan; **AND**
- II. Member has shown a response in the first 6 months of the IGF-1 therapy (e.g. increase in height, increase in height velocity); **AND**
- III. Member has evidence of non-closure of the epiphyseal plate, confirmed by radiograph

Supporting Evidence

- I. Mecasermin (Increlex) is for the long-term treatment of growth failure in children with severe primary insulin-like growth factor-1 (IGF-1) deficiency (primary IGFD) or with growth hormone (GH) gene deletion who have developed neutralizing antibodies to GH. Severe primary IGFD is defined by:
 - Height standard deviation score ≤ -3.0
 - Basal IGF-1 standard deviation score ≤ -3.0
 - Normal or elevated GH
- II. Insulin-like growth factor (IGF-1) is the principal hormonal mediator of statural growth. Under normal circumstances, growth hormone (GH) binds to its receptor in the liver and other tissues, and stimulates the synthesis/secretion of IGF-1.
 - In target tissues, the type 1 IGF-1 receptor, which is homologous to the insulin receptor, is activated by IGF-1, leading to intracellular signaling, which stimulates multiple processes leading to statural growth.
 - The metabolic actions of IGF-1 are, in part, directed at stimulating the uptake of glucose, fatty acids, and amino acids so that metabolism supports growing tissues.
- III. Severe primary IGF-1 deficiency includes members with mutations in the GH receptor (GHR), post-GHR signaling pathway, and IGF-1 gene defects; they are not GH deficient; therefore, they cannot be expected to respond adequately to exogenous GH treatment.
- IV. Mecasermin (Increlex) is not a substitute to growth hormone (GH) for approved GH indication.
- V. Mecasermin (Increlex) is not indicated for use after epiphyseal closure.

Investigational Use

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- I. Mecasermin (Increlex) is not intended for use in members with secondary forms of IGF-1 deficiency, such as GH deficiency, malnutrition, hypothyroidism, or chronic treatment with pharmacologic doses of anti-inflammatory steroids.

References

1. Increlex [package insert]. Cambridge, MA: Ipsen Biopharmaceuticals, Inc; 2019.
2. UpToDate, Inc. Growth hormone insensitivity syndromes. UpToDate [database online]. Waltham, MA. Updated March 8, 2019. Available at: <http://www.uptodate.com/home/index.html>. Accessed November 9, 2019.

Policy Implementation/Update:

Date Created	September 2008
Date Effective	October 2008
Last Updated	November 2019
Last Reviewed	12/2008, 11/2019

Action and Summary of Changes	Date
Criteria updated to new policy format. Specific changes include: removal of bone age requirement (If male, bone age is less than 16 years of age; or if female, bone age is less than 14 years of age) and update on child 2 years of age or older.	11/2019

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP134

Description

Mechlorethamine (Valchlor) is a topical nitrogen analog of sulfur mustard and is a biologic alkylating agent.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
mechlorethamine (Valchlor)	0.016% topical gel/jelly	Mycosis fungoides-type cutaneous T-cell lymphoma, in those that have received prior skin-directed therapy	60 grams (1 tube)/30 days

Initial Evaluation

- I. Mechlorethamine (Valchlor) 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. Will not be used in combination with bexarotene (Targretin); **AND**
 - D. A diagnosis of **cutaneous T-cell lymphoma** when the following are met:
 1. The disease is stage IA or IB (i.e., limited, localized); **AND**
 2. The member is relapsed, refractory, or intolerant to at least one other skin-directed therapy (e.g., corticosteroids, phototherapy, imiquimod, topical retinoids, carmustine, local radiation).
- II. Mechlorethamine (Valchlor) is considered investigational when used for all other conditions, including but not limited to:
 - A. Contact dermatitis
 - B. Non-Hodgkin lymphoma
 - C. Lichen planopilaris

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 dermatologist; **AND**
- IV. Member has exhibited response to therapy such as improvement in CAILS score, decrease in affected surface area, or decrease in plaque/scale elevation or severity.

Supporting Evidence

- I. Mechlorethamine (Valchlor) gel was assessed in a randomized, observer-blinded, active-controlled (versus compounded mechlorethamine ointment), non-inferiority clinical trial of subjects with stage IA, IB, and II A mycosis fungoides-type cutaneous T-cell lymphoma. Subjects had received at least one prior skin-directed therapy, including the following: topical corticosteroids, phototherapy, bexarotene (Targretin) gel, topical nitrogen mustard. The median number of prior therapies was two. Mechlorethamine (Valchlor) was applied topically on a daily basis for 12 months. Subjects were evaluated for a response on a monthly basis for the first six months and then every two months for the last six months using the Composite Assessment of Index Lesion Severity (CAILS) score. This score is obtained by adding the severity score of each of the following categories for up to five index lesions: erythema, scaling, plaque elevation, and surface area. Response was defined by a 50% or greater reduction in baseline score. A complete response was defined as achieving a score of 0. Subjects were also evaluated using the Severity Weighted Assessment Tool (SWAT). The SWAT score is derived by measuring each involved area as a percentage of total body surface area (% BSA) and multiplying it by a severity weighting factor. Response was defined as a 50% or greater reduction in baseline SWAT score. Sixty percent of subjects achieved a response in CAILS score versus 48% with the comparator arm. For the SWAT score, 50% in the mechlorethamine (Valchlor) arm met criteria for response versus 46% of the comparator arm. Mechlorethamine (Valchlor) statistical non-inferiority was met.
- II. The mean average daily use in the trial was 1-2 tubes per month. The cost of one tube of mechlorethamine (Valchlor) is \$4,000-\$5,000 per month; thus for a quantity exception to be considered, clinical review of body surface area affected, application amount, frequency, adherence, etc. is warranted.

Investigational or Not Medically Necessary Uses

- I. Mechlorethamine (Valchlor) has not been sufficiently evaluated for safety and/or efficacy in the following settings:
 - A. Contact dermatitis
 - B. Non-Hodgkin lymphoma
 - C. Lichen planopilaris

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References

1. Valchlor [Prescribing Information]. Malvern, PA: Ceptaris Therapeutics, Inc. August 2013.
2. Lessin SR, Duvic M, Guitart J, et al. Topical chemotherapy in cutaneous T-cell lymphoma: positive results of a randomized, controlled, multicenter trial testing the efficacy and safety of a novel mechlorethamine, 0.02%, gel in mycosis fungoides. JAMA Dermatol. 2013;149(1):25-32.

Policy Implementation/Update:

Date Created	January 2014
Date Effective	March 2014
Last Updated	November 2019
Last Reviewed	11/2019

Action and Summary of Changes	Date
Prior authorization criteria transitioned to policy format. Criteria updated to allow for oncologist prescribing. Renewal criteria changed to require specialist prescriber and specified parameters for improvement.	11/2019

Policy Type: QE

Pharmacy Coverage Policy: UMP233

Description

All medications covered by this policy work to induce catharsis by the osmotic effects of the unabsorbed sulfate salts and polyethylene glycol (PEG) in the GI tract. Specifically, sulfate salts provide sulfate anions, which are poorly absorbed, and PEG, which is primarily unabsorbed, causes water to be retained in the GI tract resulting in watery diarrhea.

Length of Authorization

- Initial: One time with each request*
*Can be approved multiple times, as requested by provider, if policy is met
- Renewal: See "Initial" Authorization

Medications Included in this Policy

Product Name	Dosage Form	Indication
All therapies with the FDA approval for use in colonoscopy preparation	Multiple	Colonoscopy preparation

Initial Evaluation

- Colonoscopy preparation medications** may be considered medically necessary when the following criteria are met:
 - Medication requested is being used as bowel preparation for colonoscopy
- Colonoscopy preparation medications are excluded when the following criteria is met:
 - Use is for treatment of constipation

Renewal Evaluation

- See initial evaluation.

Supporting Evidence

- In compliance with the United States Preventative Services Task Force (USPSTF), FDA-approved bowel preparations (non-OTC) are covered at a zero-cost share for up to 2 fills per year for members between the ages of 50-75 years with a valid prescription. The purpose of this policy is to review requests exceeding 2 fills per year to ensure use in preparation for a colonoscopy before allowing payment at a zero-cost share.

References

1. United States Department of Labor. FAQ About Affordable Care Act Implementation (Part 31). April 20, 2016. Accessed via <https://www.dol.gov/ebsa/faqs/faq-aca31.html> on July 30, 2016.
2. Facts & Comparisons. Bowel Evacuants. Accessed via <http://online.factsandcomparisons.com/MonoDisp.aspx?monoid=fandc-hcp10331&book=DFC> on July 30, 2016.

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated requirement for medication used to cover all use for colonoscopy prep instead of just in the setting of colorectal cancer screening	08/2021
Criteria transitioned to policy format	05/2021
Criteria created	07/2016

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP046

Description

Mepolizumab (Nucala) is a subcutaneously administered monoclonal antibody (IgG1 Kappa) that antagonizes interleukin-5 (IL-5).

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
mepolizumab (Nucala)	Asthma (severe)	100 mg/mL syringe, 100 mg/mL autoinjector	1 syringe/autoinjector/28 days
	Eosinophilic granulomatosis with polyangiitis		3 syringes/autoinjectors/28 days
	Hypereosinophilic Syndrome		3 syringes/autoinjectors/28 days
	Chronic Rhinosinusitis with Nasal Polyps		1 syringe/autoinjector/28 days
	Chronic obstructive pulmonary disease (moderate to severe)		1 syringe/autoinjector/28 days
	Asthma (severe)	40mg/0.4mL prefilled syringe	1 syringe/28 days
Provider Administered Agents*, **			
mepolizumab (Nucala)	Asthma (severe)	100 mg/vial	1 vial/28 days
	Eosinophilic granulomatosis with polyangiitis		3 vials/28 days
	Hypereosinophilic Syndrome		3 vials/28 days
	Chronic Rhinosinusitis with Nasal Polyps		1 vial/28 days
	Chronic obstructive pulmonary disease (moderate to severe)		1 vial/28 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.

**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

- Mepolizumab (Nucala)** may be considered medically necessary when the following criteria below are met:

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- A. Medication is prescribed by, or in consultation with, a dermatologist or a physician specializing in allergy, pulmonology, immunology, rheumatology, or ENT (ear, nose, throat); **AND**
- B. Must not be used in combination with another monoclonal antibody (e.g., benralizumab, dupilumab, omalizumab, reslizumab, etc.); **AND**
- C. A diagnosis of one of the following:
 - 1. **Asthma (severe); AND**
 - i. Member is six years of age or older; **AND**
 - ii. Member has **SEVERE** asthma as defined by one of the following:
 - a. Symptoms throughout the day
 - b. Nighttime awakenings, often 7x/week
 - c. SABA (e.g. albuterol, levalbuterol) use for symptom control occurs several times per day
 - d. Extremely limited normal activities
 - e. Lung function (percent predicted FEV1) <60%
 - f. Exacerbations requiring oral systemic corticosteroids are generally more frequent and intense relative to moderate asthma; **AND**
 - iii. Member must have asthma with an eosinophilic phenotype defined as blood eosinophils ≥ 300 cells/ μ L within previous 12 months OR ≥ 150 cells/ μ L within 6 weeks of dosing; **AND**
 - iv. 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); **OR**
 - v. Member is dependent on oral corticosteroids for asthma control; **AND**
 - vi. Member is currently being treated with:
 - a. A medium- to high-dose, or maximally tolerated inhaled corticosteroid (ICS) [e.g., budesonide, fluticasone, mometasone]; **AND**
 - i. 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}, leukotriene receptor antagonist [e.g., Singular], or theophylline); **OR**
 - b. A maximally tolerated ICS/LABA combination product (e.g., Advair, Airduo, Breo, Dulera, Symbicort); **AND**
 - vii. Background controller medications (e.g., Advair, Airduo, Breo, Dulera, Symbicort) will be continued with the use of mepolizumab (Nucala), unless contraindicated; **OR**
 - 2. **Eosinophilic Granulomatosis with Polyangiitis (EGPA); AND**
 - i. Member is 18 years of age or older; **AND**
 - ii. Member has a confirmed diagnosis of EGPA (aka Churg-Strauss Syndrome) as defined by ALL of the following:
 - a. History or presence of asthma; **AND**

- b. Blood eosinophil level 10% or an absolute eosinophil count >1000 cells/mm³; **AND**
- c. TWO or more of the following:
 - i. Histopathologic evidence of eosinophilic vasculitis, perivascular eosinophilic infiltration or eosinophil rich granulomatous inflammation
 - ii. Neuropathy
 - iii. Pulmonary infiltrates
 - iv. Sinonasal abnormalities
 - v. Cardiomyopathy
 - vi. Glomerulonephritis
 - vii. Alveolar hemorrhage
 - viii. Palpable purpura
 - ix. Antineutrophil Cytoplasmic Antibody (ANCA) positivity;**AND**
- iii. History of ONE of the following:
 - a. At least one confirmed EGPA relapse within the past two years
 - b. Failure to attain remission following induction treatment with a standard regimen (e.g., high-dose glucocorticoids with or without immunosuppressive agents [e.g., methotrexate, mycophenolate mofetil, etc.]
 - c. Recurrence of EGPA symptoms while tapering oral corticosteroid;**AND**
- iv. Member has been on stable doses of concomitant oral corticosteroid therapy for at least 4 weeks (i.e., prednisone or prednisolone at a dose of 7.5 mg/day); **AND**
- v. Physician has assessed baseline disease severity utilizing an objective measure/tool (e.g., Birmingham Vasculitis Activity Score [BVAS], history of asthma symptoms and/or exacerbations duration of remission or rate of relapses, etc.); **OR**
- 3. **Hypereosinophilic Syndrome (HES); AND**
 - i. Member is 12 years of age or older; **AND**
 - ii. Provider attests to ALL of the following:
 - a. Member has been diagnosed with HES for at least 6 months prior to starting treatment; **AND**
 - b. Member is confirmed to have F1P1L1-PDGFR α kinase-negative disease; **AND**
 - c. Member does NOT have non-hematologic secondary HES (e.g., drug hypersensitivity, parasitic helminth infection, HIV infection, non-hematologic malignancy); **AND**
 - d. Background HES therapy (e.g., oral corticosteroid, immunosuppressive, and/or cytotoxic therapy) will be continued with the use of mepolizumab (Nucala), unless contraindicated;**AND**

- iii. Member must have ALL of the following:
 - a. Two or more HES flares (see Supporting Evidence below) in the previous year; **AND**
 - b. Blood eosinophils ≥ 1000 cells/ μ L within 4 weeks of dosing; **AND**
 - c. Has been on stable doses of at least one other HES therapy (e.g., oral corticosteroids, immunosuppressive agents [hydroxyurea, cyclosporine, methotrexate, tacrolimus, azathioprine], cytotoxic therapy [imatinib], etc) for at least 4 weeks; **OR**
- 4. **Chronic Rhinosinusitis with Nasal Polyps (CRSwNP); AND**
 - i. Member is 18 years of age or older; **AND**
 - ii. Provider attests that the member has ALL of the following:
 - a. Diagnosis of bilateral sinonasal polyposis as evidenced by an endoscopy or computed tomography (CT); **AND**
 - b. Member has impaired Health-Related Quality of Life due to ongoing nasal congestion, blockage, or obstruction with moderate to severe symptom severity; **AND**
 - c. Member has at least one of the following symptoms:
 - i. Nasal discharge
 - ii. Facial pain or pressure
 - iii. Reduction or loss of smell; **AND**
 - iii. Provider attestation or clinical documentation of current persistent symptomatic nasal polyps despite maximal treatment with an intranasal corticosteroid, unless ineffective, not tolerated, or contraindicated; **AND**
 - iv. Background intranasal corticosteroids (e.g., beclomethasone [Qnasl], budesonide [Rhinocort], ciclesonide [Omnaris; Zetonna], flunisolide, fluticasone [Flonase], mometasone [Nasonex], triamcinolone [Nasacort]) will be continued with the use of Nucala, unless contraindicated; **OR**
- 5. **Chronic obstructive pulmonary disease (COPD); AND**
 - i. Member is 18 years of age or older; **AND**
 - ii. Member has a confirmed diagnosis of moderate to severe COPD with an eosinophilic phenotype defined by all of the following:
 - a. Post-bronchodilator FEV1/FVC ratio of <0.7 ; **AND**
 - b. Post-bronchodilator FEV1 % predicted $\geq 30\%$ and $<80\%$; **AND**
 - c. Documentation of blood eosinophils ≥ 300 cells/ μ L within the last 12 months; **AND**
 - iii. Member is in COPD treatment Group E defined by one of the following:
 - a. ≥ 2 moderate exacerbation(s) (e.g., treated with short-acting bronchodilators and oral corticosteroids $\pm$ antibiotics); **OR**
 - b. ≥ 1 severe exacerbation(s) (e.g., required hospitalization or emergency room visit) within the last 12 months; **AND**
 - iv. Member is currently being treated with:
 - a. A triple therapy inhaler regimen comprising of a long-acting beta-2 agonist [LABA], a long-acting muscarinic antagonist [LAMA], and an inhaled corticosteroid (ICS), unless ICS is contraindicated, such as:

- i. LABA/LAMA/ICS combination product (e.g., Trelegy Ellipta, Breztri Aerosphere); **OR**
 - ii. LABA/LAMA combination product (e.g., Anoro Ellipta, Stiolto Respimat, Bevespi Aerosphere); **AND**
 - 1. ICS has been contraindicated or not tolerated (e.g., beclomethasone (Qvar), budesonide (Pulmicort), ciclesonide (Alvesco), fluticasone (Arnuity, Flovent), mometasone (Asmanex)); **AND**
 - v. Background controller medications (e.g., Trelegy, Anoro, Stiolto, Bevespi) will be continued with the use of mepolizumab (Nucala), unless contraindicated.
- II. Mepolizumab (Nucala) is considered investigational when used for all other conditions, including but not limited to:
 - A. Non-severe, non-eosinophilic phenotype asthma
 - B. GPA (Wegener's granulomatosis) with polyangiitis
 - C. MPA (microscopic polyangiitis)
 - D. HES (hypereosinophilic syndrome) with F1P1L1-PDGFR α kinase-positive disease
 - E. Acute rhinosinusitis or Chronic Rhinosinusitis WITHOUT nasal polyps

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. Must not be used in combination with another monoclonal antibody (e.g., benralizumab, dupilumab, omalizumab, reslizumab, etc.); **AND**
- IV. A diagnosis of one of the following:
 - A. **Asthma (severe); AND**
 - i. Member has exhibited improvement or stability of disease symptoms (e.g., reduced asthma exacerbations, FEV1, reduced systemic corticosteroid requirements, reduced hospitalizations); **AND**
 - ii. Background controller medications (e.g., Advair, Airduo, Breo, Dulera, Symbicort) will be continued with the use of mepolizumab (Nucala), unless contraindicated; **OR**
 - B. **Eosinophilic Granulomatosis with Polyangiitis; AND**
 - 1. Member has exhibited improvement or stability of disease symptoms as evidenced in one or more of the following:
 - 1. Member is in remission [defined as a Birmingham Vasculitis Activity Score (BVAS) score=0 and a prednisone/prednisolone daily dose of ≤ 7.5 mg]
 - 2. Decrease in maintenance dose of systemic corticosteroids
 - 3. Improvement in BVAS score compared to baseline
 - 4. Improvement in asthma symptoms or asthma exacerbations

5. Improvement in duration of remission or decrease in the rate of relapses;
OR
- C. **Hypereosinophilic Syndrome; AND**
 1. Member has exhibited improvement or stability of disease symptoms (e.g., reduction in HES flares, improved fatigue, reduced oral corticosteroid requirements, decreased eosinophil levels); **OR**
- D. **Chronic Rhinosinusitis with Nasal Polyps (CRSwNP); AND**
 1. Member has exhibited improvement or stability of disease symptoms (e.g., improvement in nasal congestion/obstruction severity, reduction in nasal polyps, improvement in sense of smell); **AND**
 2. Background intranasal corticosteroids (e.g., beclomethasone [Qnasl], budesonide [Rhinocort], ciclesonide [Omnaris; Zetonna], flunisolide, fluticasone [Flonase], mometasone [Nasonex], triamcinolone [Nasacort]) will be continued with the use of Nucala, unless contraindicated; **OR**
- E. **Chronic obstructive pulmonary disease; AND**
 - i. Member has exhibited improvement or stability of disease symptoms (e.g., reduced COPD exacerbations, reduced hospitalizations, improved FEV1); **AND**
 - ii. Background controller medications (e.g., LAMA/LABA/ICS products (e.g., Trelegy Ellipta, Breztri Aerosphere) or LABA/LAMA products (e.g., Anoro Ellipta, Stiolto Respimat, Bevespi Aerosphere) will be continued with the use of mepolizumab (Nucala), unless contraindicated

Supporting Evidence

- I. There is a lack of evidence supporting treatment with dual use of biologic therapies and a potential for increased risk of side effects.
- II. Mepolizumab (Nucala) is indicated as an add-on maintenance treatment for members 6 years and older with a diagnosis of severe eosinophilic asthma (SEA), treatment for adult members with eosinophilic granulomatosis with polyangiitis, and treatment for members 12 years and older with hypereosinophilic syndrome for at least 6 months without an identifiable non-hematologic secondary cause. The age expansion approval by the FDA from 12 years of age to 6 years of age in children with a diagnosis of SEA was based on an open-label study that was conducted in children aged 6 to 11 years of age with SEA. In this study, pharmacokinetics, pharmacodynamics, and long-term safety were evaluated and determined to be consistent with the known safety profile associated with members aged 12 years and older.
- III. The FDA approval of mepolizumab (Nucala) in the setting of severe eosinophilic asthma was evaluated in 3 randomized, placebo controlled, multicenter trials of 24 to 52 weeks in duration. The primary outcome was the rate of exacerbation, and it was reduced by 47% (95% confidence interval [CI], 28 to 60) among members receiving intravenous mepolizumab and by 53% (95% CI, 36 to 65) among those receiving subcutaneous mepolizumab, as compared with those receiving placebo (P<0.001 for both comparisons). The members enrolled in this trial were 12 to 82 years of age.
 - Trial inclusion criteria required patients to have a history of 2 or more exacerbations requiring systemic corticosteroids in the previous year despite regular use of high-dose ICS plus additional controller(s) with, or without, oral corticosteroids (OCS). Patients were required to have at least 1 of the following

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4 prespecified criteria in the previous 12 months: blood eosinophil count ≥ 300 cells/mcL, sputum eosinophil count $\geq 3\%$, exhaled nitric oxide concentration ≥ 50 ppb, or deterioration of asthma control after $\leq 25\%$ reduction in regular maintenance ICS/OCS.

- IV. The FDA approval of mepolizumab (Nucala) in the setting of eosinophilic granulomatosis with polyangiitis was evaluated in a multicenter, double-blind, parallel-group, phase 3 trial. The two primary end points were the accrued weeks of remission over a 52-week period, according to categorical quantification, and the proportion of participants in remission at both week 36 and week 48. In the mepolizumab treatment arm, there was significantly more accrued weeks of remission than placebo (28% vs. 3% of the participants had ≥ 24 weeks of accrued remission; odds ratio, 5.91; 95% confidence interval [CI], 2.68 to 13.03; $P < 0.001$) and a higher percentage of participants in remission at both week 36 and week 48 (32% vs. 3%; odds ratio, 16.74; 95% CI, 3.61 to 77.56; $P < 0.001$). The members that were enrolled in this trial were at least 18 years of age.
- V. The FDA approval of mepolizumab (Nucala) in the setting of hypereosinophilic syndrome was evaluated in a phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter trial. Patients were randomized 1:1 to receive mepolizumab (Nucala) or placebo, plus an existing HES therapy. The primary endpoint evaluated the proportion of patients who experienced a flare during the 32-week study period compared to placebo, which was 28% compared to 56% (OR 0.28, 95% CI 0.12- 0.64, $p = 0.002$). The patients enrolled in this trial were at least 12 years of age.
 - Trial inclusion criteria required patients to have F1P1L1-PDGFR α -negative HES for at least 6 months, uncontrolled HES (defined as a history of at least 2 flares within the past 12 months and blood eosinophil count > 1500 cells/ μ L and/or tissue eosinophilia), blood eosinophil count > 1000 cells/ μ L, on stable background HES therapy (includes, but not limited to, oral corticosteroid [OCS], immunosuppressive, and/or cytotoxic therapy) for at least 4 weeks before randomization.
 - HES flare defined as:
 - i. An HES-related clinical manifestation, based on a physician-documented change in clinical signs or symptoms, necessitating an increase in the maintenance OCS dose > 10 mg prednisone equivalent/day for 5 days OR an increase in/addition of any cytotoxic and/or immunosuppressive HES therapy; OR
 - ii. Receipt of 2+ courses of blinded OCS during the treatment period
- VI. The Global Initiative for Asthma (GINA) 2020 update recommends the addition of respiratory biologics, with respect to their allergic biomarkers after inadequate asthma control despite good adherence and inhaler technique on maximized Step 4 (medium dose ICS-LABA) or Step 5 (high dose ICS-LABA) therapy. Other controller options for Step 4 include high dose ICS-LABA, add-on tiotropium, or add-on leukotriene receptor antagonist (LTRA). Other controller options for Step 5 include add-on anti-IL5 or add-on low dose OCS, although guidelines note to consider side effects.
- VII. Chronic rhinosinusitis (CRS) is defined as an inflammatory condition involving the paranasal sinuses and linings of the nasal passages, which persists for 12 weeks or longer per both the American Academy of Allergy Asthma and Immunology (AAAAI) and the American Academy of Otolaryngology-Head and Neck (AAO-HN) guidelines. The diagnosis requires at least two of four cardinal signs/symptoms (mucopurulent drainage, nasal obstruction, facial pain/pressure/fullness, and decreased sense of smell). Goals of therapy include control of mucosal inflammation and edema, maintenance of adequate sinus ventilation and drainage,

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treatment of colonizing or infection micro-organisms, if present, and reduction in the number of acute exacerbations. A significant proportion of patients also have nasal polyps (CRSwNP), roughly 25-30% of those with just CRS, and the standard of care includes intranasal corticosteroids, intranasal saline, oral corticosteroids in short burst therapy, and oral antibiotics if needed.

- VIII. A total of 407 patients with CRSwNP were evaluated in one randomized, placebo-controlled, multicenter, 52-week treatment trial (SYNAPSE Study). Patients received mepolizumab (Nucala) 100 mg or placebo subcutaneously once every 4 weeks. Patients had recurrent and symptomatic CRSwNP and had at least one surgery for the removal of nasal polyps within the previous 10 years. Patients were required to have nasal obstruction symptoms with a visual analog scale (VAS) score of >5 out of a maximum score of 10. Patients were also required to have an endoscopic bilateral nasal polyp score (NPS) of ≥ 5 out of 8 with NPS ≥ 2 in each nasal cavity. Of the patients enrolled, 35% were female, 93% were White, with ages ranged from 18 to 82 years, a mean VAS score of 9 on a scale of 0-10, and a mean bilateral endoscopic NPS of 5.5 on a scale of 0-8. The co-primary endpoints were change from baseline to Week 52 in total endoscopic NPS (0 to 8 scale) as graded by independent blinded assessors and change from baseline in nasal obstruction VAS score (0 to 10 scale) during Weeks 49 to 52. The key secondary endpoint was the time to first nasal surgery (nasal polypectomy) up to Week 52 in this trial.
- IX. Patients who received mepolizumab (Nucala) 100 mg met a statistically significant improvement (decrease) in bilateral NPS at Week 52 and nasal obstruction VAS score from Weeks 49 to 52 at the end of the 52-week treatment period. See below table.

Scores (range)	Placebo n=201		Mepolizumab (Nucala) n=206		Mean Difference vs. Placebo (95% CI)
	Baseline Mean (SD)*	Mean Change (SE) ^o	Baseline Mean (SD)*	Mean Change (SE) ^o	
NPS (0-8)	5.6 (1.41)	0.06 (0.14)	5.4 (1.17)	-0.87 (0.14)	-0.93 (-1.31, -0.55)
Nasal obstruction VAS (0-10)	9.02 (0.83)	-2.54 (0.25)	8.92 (0.83)	-4.40 (0.25)	-1.86 (-2.53, 1.19)

* SD- standard deviation; ^o SE- standard error

- X. The AAAA-I, AAO-HN, and the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2020, recommend intranasal corticosteroids to be continued and mepolizumab (Nucala) to be add-on therapy.
- XI. The FDA approval of mepolizumab (Nucala) in the setting of chronic obstructive pulmonary disease (COPD) was evaluated in two randomized, double-blind, placebo-controlled, multicenter trials of 52 up to 104 weeks in duration (MATINEE and METRIX). Both trials evaluated mepolizumab 100 mg once weekly as add-on treatment to existing triple therapy in the treatment of COPD in comparison to placebo. The clinical trials included patients 40 years of age and older, diagnosis of COPD for at least 1 year prior to screening, moderate to severe airflow limitation defined as FEV1/FVC ratio < 0.7 and post-bronchodilator FEV1 of 20%-80% predicted, history of at least 2 moderate exacerbations or 1 severe exacerbation, and patients were receiving triple therapy for at least 3 months prior to screening. Patients in the MATINEE trial were required to have a minimum blood eosinophil count of 300 cells/uL at screening; meanwhile, the METRIX trial did not have a minimum blood eosinophil count, but the patients were stratified based on their eosinophil count at baseline: ≥ 150 cells/uL at screening, ≥ 300 cells/uL in the previous 12 months, or < 150 cells/uL at screening with no evidence of blood eosinophil count ≥ 300 cells/uL in the previous 12 months (insufficient data to support use of mepolizumab in this population; they were not included in the efficacy analysis of the two trials). The primary outcome was the annual rate of moderate to severe exacerbation.

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Exacerbations were considered moderate if treatment with systemic glucocorticoids, antibiotics, or both were needed and severe exacerbations resulted in hospitalization for at least 24 hours, emergency department visit for at least 24 hours, or death. The MATINEE trial demonstrated an annualized rate of 0.80 (rate ratio 0.79; 95% CI 0.66-0.94, p-value 0.01) and the METRIX trial demonstrated an annualized rate of 1.40 (rate ratio 0.82; 95% CI 0.68-0.98, p-value 0.04) compared to placebo. Secondary endpoints included time-to-first event (i.e., moderate to severe exacerbation) and health-related quality of life assessments (e.g., SGRQ, CAT, etc.). The only significant finding for both trials was the time-to-first event, in which mepolizumab demonstrated a significantly longer duration (MATINEE 419 days vs. 321 days; hazard ratio 0.77 (0.64-0.93), p-value 0.009) (METRIX 192 days vs. 141 days; hazard ratio 0.75 (0.60-0.94), p-value 0.04). The safety profiles for mepolizumab and placebo were similar across both trials with the most common adverse events reported being exacerbations or worsening of COPD, nasopharyngitis, headache, and pneumonia. Overall, 46/820 (5%) patients discontinued mepolizumab treatment due to an adverse event. The adverse events weren't specified. Twenty-seven deaths occurred during the treatment period although it wasn't specified how many were due to treatment.

- XII. The Global Initiative for Chronic Obstructive Lung Disease (GOLD): Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease 2025 update mentions mepolizumab is being investigated in patients with COPD, who had a history of two or more exacerbations in the last year and increased blood eosinophil count. The guidelines note there are large, randomized trials being conducted to investigate whether mepolizumab (Nucala) and other biologic therapies are effective in a population with evidence of eosinophilic or type II airway inflammation.

Investigational or Not Medically Necessary Uses

- I. Mepolizumab (Nucala) has not been adequately studied for the following conditions and does not have established safety and efficacy in these populations:
 - A. Non-severe, non-eosinophilic phenotype asthma
 - i. Mepolizumab (Nucala) has not been studied in members with non-severe, non-eosinophilic phenotype asthma; therefore, it would be considered investigational when Nucala is requested in that setting.
 - B. GPA (Wegener's granulomatosis) with polyangiitis and MPA (microscopic polyangiitis)
 - i. Both GPA and MPA diagnoses were excluded in the phase 3 trial (A Study to Investigate Mepolizumab in the Treatment of Eosinophilic Granulomatosis with Polyangiitis).
 - C. HES (hypereosinophilic syndrome) with F1P1L1-PDGFR α kinase-positive disease
 - i. Mepolizumab (Nucala) has not been studied in members with F1P1L1-PDGFR α kinase-positive disease; therefore, it would be considered investigational when Nucala is requested in this setting.

References

1. Nucala [Prescribing Information]. Philadelphia, PA: GlaxoSmithKline LLC. Updated May 2025. Accessed May 2025.
2. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab Treatment in Members with Severe Eosinophilic Asthma. *N Engl J Med* 2014; 371:1198-1207. DOI: 10.1056/NEJMoa1403290.
3. Wechsler ME, Akuthota P, Jayne D, et al. Mepolizumab or Placebo for Eosinophilic Granulomatosis with Polyangiitis. *N Engl J Med* 2017; 376:1921-1932. DOI: 10.1056/NEJMoa1702079.

4. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2020 Update. Available from: <http://www.ginasthma.org>. Accessed January 2021.
5. Roufosse F, Kahn JE, Rothenberg ME, et al. Efficacy and safety of mepolizumab in hypereosinophilic syndrome: A phase III, randomized, placebo-controlled trial. *J Allergy Clin Immunol* 2020;146(6):1397-1405. DOI: 10.1016/j.jaci.2020.08.037.
6. Han JK, Bachert C, Fokkens W, et al. Mepolizumab for chronic rhinosinusitis with nasal polyps (SYNAPSE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med*. 2021 Apr 16:S2213-2600(21)00097-7. doi: 10.1016/S2213-2600(21)00097-7. Epub ahead of print. PMID: 33872587.
7. American Academy of Otolaryngology- Head and Neck Surgery Adult Sinusitis Guidelines: [Adult Sinusitis - Clinical Practice Guideline \(aafp.org\)](#)
8. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. *Rhinology*. 2020 Feb 20;58(Suppl S29):1-464. doi: 10.4193/Rhin20.600. PMID: 32077450. https://epos2020.com/Documents/supplement_29.pdf
9. American Academy of Allergy Asthma and Immunology Rhinitis 2020 Clinical Update: [Rhinitis 2020: A practice parameter update \(aaaai.org\)](#)
10. Sciurba FC, Criner GJ, Christenson SA, et al. Mepolizumab to Prevent Exacerbations of COPD with an Eosinophilic Phenotype. *N Engl J Med*. 2025;392(17):1710-1720. doi:10.1056/NEJMoa2413181
11. Pavord ID, Chanez P, Criner GJ, et al. Mepolizumab for Eosinophilic Chronic Obstructive Pulmonary Disease. *N Engl J Med*. 2017;377(17):1613-1629. doi:10.1056/NEJMoa1708208
12. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for Prevention, Diagnosis, and Management of COPD: 2025 Report. Available from: <https://goldcopd.org>. Accessed May 2025.

Policy Implementation/Update:

Action and Summary of Changes	Date
Added relapse history criteria for EGPA. Removed oral steroid requirement for CRSwNP. Removed blood eosinophil level requirement for EGPA. Added path to coverage for oral steroid dependence in severe asthma.	03/2025
Added 40mg prefilled syringe	02/2022
Policy updated to reflect the new CRSwNP indication.	09/2021
Policy updated to reflect the new HES indication. Updated renewal length of authorization from 6 month to 12 months. Also added prescribed by or in consultation with a specialist requirement. For initial criteria: asthma: revised “severe eosinophilic asthma” verbiage to “asthma (severe)” in attempts to align with other respiratory biologic policies, revised verbiage for add-on maintenance treatment requirements to medium- to high-dose, or maximally tolerated ICS and one additional asthma controller medication OR maximally tolerated ICS/LABA combination, added requirement of continued use with background controller medications. For renewal criteria: removed criteria requirement confirming lack of toxicity to therapy; added “member has received a previous prior authorization approval for this agent through this health plan; AND member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise.”; asthma: reformatted renewal criteria and added member exhibition of “stability” in addition to improvement of disease symptoms, added environmental triggers and continued background controller medications for asthma renewal criteria; EGPA: updated verbiage to “member has exhibited improvement or stability of disease symptoms”. For supporting evidence: for asthma, added trial inclusion criteria and GINA 2020 guideline recommendations.	03/2021
Policy updated to reflect the newly approved age expansion for SEA from members 12 years and older to 6 years or older. Also added leukotriene modifiers as an example of a controller medication per GINA guidelines. To the EGPA section, examples of an objective measure/tool were added to align with renewal criteria and changed classification criteria for eosinophils to > 10% per ACR classification.	10/2019
New Policy	06/2019

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP093

Description

Metreleptin (Myalept) is a leptin analog that binds to and activates the human leptin receptor as replacement therapy to treat generalized lipodystrophy due to congenital or acquired generalized lipodystrophy.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
metreleptin (Myalept)	11.3 mg powder (5 mg/mL) vial	Congenital Lipodystrophy; Acquired Generalized Lipodystrophy	60 mL/30 days

Initial Evaluation

- I. Metreleptin (Myalept) may be considered medically necessary when the following criteria below are met:
 - A. Member is one year of age or older; **AND**
 - B. Medication is prescribed by, or in consultation with, an endocrinologist; **AND**
 - C. A diagnosis of **Congenital Lipodystrophy OR Acquired Generalize Lipodystrophy** when the following are met:
 1. Provider attests that the fasting leptin concentration at baseline is below the normal range; **AND**
 2. Member has a diagnosis of type 2 diabetes mellitus (T2DM) or insulin resistance; **AND**
 3. Member has a persistent hemoglobin A1c (HbA1c) > 7% despite dietary intervention and medication management (e.g., metformin) for T2DM; **AND**
 4. Member has a diagnosis of hypertriglyceridemia; **AND**
 5. Member has persistent triglyceride levels > 250 mg/dL despite dietary intervention and medication management for hypertriglyceridemia (e.g., fibrates, omega-3 fatty acids); **AND**
 6. Member does not have any hematologic abnormalities (e.g., leukopenia, neutropenia, bone marrow abnormalities, lymphadenopathy).
- II. Metreleptin (Myalept) is considered investigational when used for all other conditions, including but not limited to:

- A. Partial lipodystrophy
- B. Localized lipodystrophy
- C. Liver disease (e.g., nonalcoholic steatohepatitis [NASH])
- D. Human Immunodeficiency Virus (HIV) – related lipodystrophy
- E. Metabolic disease (e.g., T2DM, hypertriglyceridemia)

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through the health plan; **AND**
- II. The member is not continuing therapy based off established therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for continuation through this health plan; **AND**
- III. Member has exhibited improvement or stability of disease symptoms as defined by, a reduction from baseline for **one** of the following parameters:
 - A. HbA1c
 - B. Fasting glucose
 - C. Triglycerides; **AND**
- IV. Member does not have any hematologic abnormalities (e.g., leukopenia, neutropenia, bone marrow abnormalities, lymphadenopathy).

Supporting Evidence

- I. Although the guideline states that there is no age limit for initiation of metreleptin (Myalept), and there were reported case studies where children as young as six months have been treated, the actual pediatric inclusion population in the FDA approval of metreleptin (Myalept) was 1 to 17 years of age.
- II. According to the guideline (The Diagnosis and Management of Lipodystrophy Syndromes: A Multi-Society Practice Guideline), there is no defined serum leptin levels that have established to rule out the diagnosis of lipodystrophy. Therefore, specific lab values may not be very informative for the diagnosis of congenital or acquired generalized lipodystrophy.
- III. Members with congenital or acquired generalized lipodystrophy and T2DM, metformin is a first-line agent for diabetes and insulin resistance, along with, other considerations for antihyperglycemia agents: insulin is effective for hyperglycemia, and thiazolidinediones, which should be used with caution in generalized lipodystrophy as their efficacy has not been established in that setting.
- IV. Members with congenital or acquired generalized lipodystrophy and hypertriglyceridemia, fibrates and/or long-chain omega-3 fatty acids should be used for hypertriglyceridemia.
- V. As part of the metreleptin (Myalept) Risk Evaluation and Mitigation Strategy (REMS) program, provider will need to evaluate members with acquired generalized lipodystrophy for significant hematologic abnormalities due to the reported risk of T-cell lymphoma in that population.

Investigational or Not Medically Necessary Uses

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- I. There is limited evidence to suggest the safety and efficacy of metreleptin (Myalept) outside of the FDA-approved indications of congenital or acquired generalized lipodystrophy. Additionally, the following indications listed below were denoted to have a “limitation of use” in the metreleptin (Myalept) package insert.
- A. Partial lipodystrophy
 - B. Liver disease (e.g., nonalcoholic steatohepatitis [NASH])
 - C. Human Immunodeficiency Virus (HIV) – related lipodystrophy
 - D. Metabolic disease (e.g., T2DM, hypertriglyceridemia)

References

1. Myalept [Prescribing Information]. Cambridge, MA: Aegerion Pharmaceuticals, Inc. August 2015.
2. Brown RJ, Araujo-Vilar D, Cheung PT, et al. The Diagnosis and Management of Lipodystrophy Syndromes: A Multi-Society Practice Guideline. The Journal of Clinical Endocrinology & Metabolism, Volume 101, Issue 12, 1 December 2016, Pages 4500–4511. Available at: <https://doi.org/10.1210/jc.2016-2466>

Policy Implementation/Update:

Date Created	September 2014
Date Effective	September 2014
Last Updated	October 2019
Last Reviewed	10/2019

Action and Summary of Changes	Date
Criteria transitioned into policy with the following updates: addition of supporting evidence, addition of investigational section along with supporting evidence, inserted lab values for type 2 diabetes and hypertriglyceridemia, added sample language to the renewal section, and assess for stability parameters upon renewal.	10/2019

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP201

Description

Metyrosine (Demser, generic) is an orally administered tyrosine hydroxylase inhibitor.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
metyrosine (Demser, generic)	pheochromocytoma	250 mg capsule	480 capsules/30 days

Initial Evaluation

- I. **Metyrosine (Demser, generic)** 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, an endocrinologist; **AND**
 - C. The request is for **generic** metyrosine; **OR**
 1. Treatment with **generic** metyrosine has been ineffective, not tolerated, or contraindicated; **AND**
 - D. A diagnosis of **pheochromocytoma** when the following are met:
 1. Member has a surgical resection planned; **AND**
 - i. Treatment with an alpha blocker (e.g., phenoxybenzamine, prazosin, terazosin, doxazosin) in combination with a beta blocker (e.g., propranolol, metoprolol, atenolol) was ineffective, contraindicated, or not tolerated; **OR**
 2. Member has a contraindication to surgery, or has malignant pheochromocytoma; **AND**
 - i. Treatment with the following has been ineffective, contraindicated, or not tolerated:
 - a. A selective alpha blocker (e.g., doxazosin, terazosin or prazosin); **AND**
 - b. Generic phenoxybenzamine
- II. Metyrosine is considered investigational when used for all other conditions, including but not limited to:
 - A. Velocardiofacial syndrome-associated psychosis
 - B. Bipolar disorder
 - C. Schizophrenia
 - D. Gilles de la Tourette's syndrome
 - E. Sarcoma

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 requires long-term pharmacologic treatment following surgery or has malignant pheochromocytoma; **AND**
- IV. Treatment with the following has been ineffective, contraindicated, or not tolerated:
 - A. A selective alpha blocker (e.g., doxazosin, terazosin or prazosin); **AND**
 - B. Generic phenoxybenzamine; **AND**
- V. Member has exhibited improvement or stability of disease symptoms [e.g., hypertension, diaphoresis, headache, palpitations, tachycardia, syncope, anxiety] while on therapy; **AND**
- VI. The request is for **generic** metyrosine; **OR**
 - A. Treatment with **generic** metyrosine has been ineffective, not tolerated, or contraindicated

Supporting Evidence

- I. Pheochromocytoma is a rare neuroendocrine tumor that hypersecrete one or more catecholamines (epinephrine, norepinephrine, and dopamine) and if left untreated, cardiovascular morbidity and mortality are high. Once diagnosed, patients should undergo surgical resection of the pheochromocytoma following appropriate medical preparation. Preop medications are used for volume expansion and to control hypertension and preventing hypertensive crisis during surgery. Patients with undiagnosed pheochromocytomas who undergo surgery for other reasons (and therefore have not undergone preoperative medical therapy), have an increased surgical mortality rate due to lethal hypertensive crises, malignant arrhythmias, and multiorgan failure. No randomized, controlled trials have compared the different approaches, and there is no universally accepted method of preparation for surgery in patients with pheochromocytoma.
- II. Guidelines recommend preoperative combined alpha and beta blockade to prevent perioperative cardiovascular complications. Both selective (e.g. phenoxybenzamine) and non-selective (e.g. doxazosin, terazosin, prazosin) alpha-blockers have been used, there is insufficient evidence to recommend one over the other. After adequate alpha blockade has been achieved, beta blockade is initiated, which typically occurs two to three days preoperatively. Metyrosine can be considered an alternative treatment option in patients who cannot be treated with the typical combined alpha and beta blockade protocol because of intolerance or cardiopulmonary reasons. Preoperative medical treatment is recommended for 7 to 14 days to allow adequate time to normalize blood pressure and heart rate.
- III. Metyrosine is FDA approved for preoperative preparation of patients for surgery, management of patients when surgery is contraindicated, or chronic treatment of patients with malignant pheochromocytoma.
- IV. The recommended initial dose of metyrosine for adults and children 12 years of age or older is 250 mg four times daily. Treatment is dosed based on clinical symptoms and catecholamine excretion and may be increased by 250 to 500 mg every day to a maximum of 4.0 grams per day in divided doses.

- V. There are no curative treatments for metastatic pheochromocytoma, unless the sites of disease are surgically resectable. Even in the metastatic setting standard treatment consists of surgery and palliative care. If all identifiable disease is resectable, including a limited number of distant metastases, surgery can provide occasional long-term remission. If disease is unresectable, surgical debulking will not improve survival; however, it is occasionally indicated for symptom relief. Per UptoDate, selective alpha-1-adrenergic blocking agents (e.g., prazosin, terazosin, or doxazosin) are utilized in many centers or are preferred to phenoxybenzamine when long-term pharmacologic treatment is indicated (e.g., for metastatic pheochromocytoma), due to their more favorable side-effect profiles and lower financial cost.
- VI. Most patients with pheochromocytoma treated with metyrosine experience decreased frequency and severity of hypertensive attacks with their associated headache, nausea, sweating, and tachycardia.
- VII. The maximum biochemical effect usually occurs within two to three days, and the urinary concentration of catecholamines and their metabolites usually returns to pretreatment levels within three to four days after treatment is discontinued. In some patients the total excretion of catecholamines and catecholamine metabolites may be lowered to normal or near normal levels (less than 10 mg/24 hours). In most patients, the duration of treatment has been two to eight weeks, but several patients have received metyrosine for periods of 1 to 10 years. Per the package insert, the total human experience with the drug is quite limited and few patients have been studied long term.

Investigational or Not Medically Necessary Uses

- I. Metyrosine has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Velocardiofacial syndrome-associated psychosis
 - i. Clinical evidence available is limited to case reports. There was a phase 2 trial (N=2) sponsored by Bausch Health (NCT01127503). However, results were not completed as the study was terminated due to enrollment, study-design and execution challenges.
 - B. Bipolar disorder
 - i. Ten patients with psychotic diseases were given metyrosine, up to 4 grams/day. Of the 7 patients with mania, 5 improved while receiving metyrosine and 3 continued to improve after the metyrosine was discontinued. All 3 patients who were being treated for depression became worse and later improved after the metyrosine was discontinued. Further evidence is needed to further evaluate and support this off label use in a space with several treatment options.
 - C. Schizophrenia
 - i. In a double-blind, crossover, placebo study severe schizophrenic symptoms could not be managed by metyrosine (2.75 grams/day). Use in this setting is not supported by available clinical evidence.
 - D. Gilles de la Tourette's syndrome
 - i. Metyrosine in doses of 1750 to 3000 milligrams/day was not an effective treatment for Gilles de la Gilles de la Tourette's syndrome. In only 2 out of 6

patients were movements greatly diminished with high doses of metyrosine. Use in this setting is not supported by available clinical evidence.

E. Sarcoma

- i. Combination therapy with a metyrosine derivative is subject of ongoing trials, currently recruiting, in this setting.

References

1. Demser [package insert]. Bridgewater, NJ. Valeant Pharmaceuticals International, Inc. December 2017
2. Uptodate. Treatment of pheochromocytoma in adults. Updated 04/22/2024.
3. Uptodate. Paraganglioma and pheochromocytoma: Management of malignant disease. Updated 02/01/2024.
4. Lenders JWM, Duh Q-Y, Eisenhofer G, et al. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014;99(6):1915-1942.
5. PDQ® Adult Treatment Editorial Board. PDQ Pheochromocytoma and Paraganglioma Treatment. Bethesda, MD: National Cancer Institute. Updated 10/16/2020. Available at: <https://www.cancer.gov/types/pheochromocytoma/hp/pheochromocytoma-treatment-pdq>. [PMID: 26389312]
6. Metyrosine. Micromedex Solutions. Truven Health Analytics, Inc. Ann Arbor, MI. Available at: <http://www.micromedexsolutions.com>.
7. Carandang CG, Scholten MC. Metyrosine in psychosis associated with 22q11.2 deletion syndrome: case report. J Child Adolesc Psychopharmacol. 2007;17(1):115-120.
8. Bausch Health Americas, Inc. Metyrosine (Demser®) for the Treatment of Psychotic Disorders in Patients with Velocardiofacial Syndrome. Available from: <http://www.clinicaltrials.gov/ct2/show/NCT01127503>. NLM identifier: NCT01127503.
9. Fishbein L, Del Rivero J, Else T, et al. The North American Neuroendocrine Tumor Society Consensus Guidelines for Surveillance and Management of Metastatic and/or Unresectable Pheochromocytoma and Paraganglioma. Pancreas. 2021;50(4):469-493. doi:10.1097/MPA.0000000000001792
10. Fassnacht M, Tsagarakis S, Terzolo M, et al. European Society of Endocrinology clinical practice guidelines on the management of adrenal incidentalomas, in collaboration with the European Network for the Study of Adrenal Tumors. Eur J Endocrinol. 2023;189(1):G1-G42. doi:10.1093/ajendo/lvad066

Policy Implementation/Update:

Action and Summary of Changes	Date
Annual review; updated references	06/2024
Added step through generic metyrosine prior to branded Demser	03/2024
Policy created	11/2020

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP094

Description

Midostaurin (Rydapt) is an orally administered tyrosine kinase inhibitor (TKI) targeting FLT3 and KIT D816V receptors to induce cell apoptosis.

Length of Authorization

- Initial: Six months
- Renewal:
 - i. AML: Cannot be renewed
 - ii. Systemic mast cell disease: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
midostaurin (Rydapt)	25 mg capsule	Acute myeloid leukemia, newly diagnosed, FLT3 mutation-positive, in combination with cytarabine/daunorubicin induction and cytarabine consolidation	56 capsules/28 days
		Systemic mast cell disease: aggressive systemic mastocytosis, systemic mastocytosis with hematological neoplasm, mast cell leukemia	224 capsules/28 days

Initial Evaluation

- I. Midostaurin (Rydapt) 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. A diagnosis of one of the following:
 1. **Acute myeloid leukemia (AML); AND**
 - i. The member has FLT3 mutation-positive AML; **AND**
 - ii. Will be used in combination with standard cytarabine and daunorubicin induction AND cytarabine consolidate therapy; **AND**
 - iii. Will not be used with any other oncolytic therapy outside of cytarabine and daunorubicin; **AND**
 - iv. The member has received no prior therapy for AML; **OR**

2. **Systemic mast cell disease; AND**
 - i. Systemic mast cell disease is characterized by one of the following: aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated hematological neoplasm (SM-AHN), or mast cell leukemia (MCL); **AND**
 - ii. Midostaurin (Rydapt) will not be used in combination with any other oncolytic medication.
- II. Midostaurin (Rydapt) is considered investigational when used for all other conditions, including but not limited to:
 - A. Pediatric leukemia
 - B. Rectal cancer
 - C. Acute myeloid leukemia in absence of FLT3 mutation

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. Midostaurin (Rydapt) is prescribed by, or in consultation with an oncologist; **AND**
 - A. For **acute myeloid leukemia**:
 - a. No renewal, one 6-month (initial) approval per lifetime.
 - B. For **systemic mast cell disease**;
 - a. Midostaurin (Rydapt) will not be used in combination with any other oncolytic medication; **AND**
 - b. Clinical documentation of response to treatment, such as stabilization or improvement of disease, and absence of unacceptable toxicity from the medication.

Supporting Evidence

- I. Midostaurin (Rydapt) was evaluated in three trials. Trial 1: in combination with chemotherapy in a randomized, double-blind, placebo-controlled trial in adults with FLT3-mutated AML. Subjects received 50 mg twice daily on days 8-21 for up to two cycles, followed by up to 12 months of midostaurin (Rydapt) therapy. Although evaluated for up to one year of therapy, the FDA-approval for midostaurin (Rydapt) indicates combination therapy with cytarabine and daunorubicin for two cycles of induction and four cycles of consolidation - for a complete total of six 28-day cycles. The primary outcome was overall survival (OS) which was statistically in favor of midostaurin (Rydapt) [HR 0.77; 95% CI 0.63-0.95, p=0.016]; however, OS data plateaued before reaching the median. Median survival could not be reliably estimated.
- II. Midostaurin (Rydapt) has not been sufficiently evaluated for safety and/or efficacy in combination with any other oncolytic medication outside of cytarabine and daunorubicin in the setting of AML.

- III. In Trial 2, midostaurin (Rydapt) was evaluated in a single-arm, open-label trial in ASM, SM-AHN, and MCL, collectively referred to as advanced SM. The trial included 116 adult subjects that had relapsed or progressed on or after 0-2 prior therapies. The primary outcome was complete remission (CR) plus incomplete remission (ICR) by six cycles via the Valent criteria for ASM and SM-AHN, with twenty-one percent of subjects meeting the primary endpoint (16-38%, depending on the specific type of SM). The median duration of CR+ICR was not reached at time of evaluation, and the median time to CR+ICR was 0.5 months.
- IV. Trial 3 was a single-arm, open-label trial of 26 subjects with advanced SM. By Valent criteria, 10 achieved a response by two cycles that was sustained for at least eight weeks.
- V. Midostaurin (Rydapt) is available in 25 mg capsules to be given as 50 mg twice daily on days 8-21 of each 28-day cycle for a total of six cycles in AML or, given as 100 mg twice daily continuously for SM.

Investigational or Not Medically Necessary Uses

- I. The safety and efficacy of midostaurin (Rydapt) has not been sufficiently established in the following settings:
 - A. Pediatric leukemia
 - B. Rectal cancer
 - C. Acute myeloid leukemia in absence of FLT3 mutation

References

1. Rydapt [Prescribing Information]. East Hanover, NJ. Novartis Pharmaceuticals Corporation. 2017.
2. Gotlib J., Kluin-Nelemans HC, George TI, et al. Efficacy and safety of midostaurin in advanced systemic mastocytosis. N Engl J Med. 2016. June 30;374(26): 2530-2541.
3. NCCN Clinical Practice Guidelines in Oncology. Acute Myeloid Leukemia. Version 2.2020. Updated September 2019. Available at: https://www.nccn.org/professionals/physician_gls/default.aspx
4. Stone RM, Mandrekar SJ, Sandfor BL, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. N Engl J Med. 2017. Aug 3;377(5): 454-464.

Policy Implementation/Update:

Date Created	July 2017
Date Effective	August 2017
Last Updated	November 2019
Last Reviewed	November 2019

Action and Summary of Changes	Date
Prior authorization criteria transitioned to policy. Age requirement added. Clarification of appropriate line of therapy required for approval. Renewal allowance removed for AML and extended to six months for SM.	11/2019

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP096

Description

Migalastat (Galafold) is a pharmacologic chaperone that binds to and stabilizes specific mutant forms of alfa-galactosidase, thereby facilitating proper trafficking of the enzyme to lysosomes and increasing enzyme activity

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
migalastat (Galafold)	123 mg capsule	Fabry disease	15 capsules/30 days

Initial Evaluation

- I. Migalastat (Galafold) 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 a specialist in genetics; **AND**
 - C. Medication will not be used in combination with Enzyme Replacement Therapy (ERT); **AND**
 - D. A diagnosis of **Fabry disease** when the following are met:
 1. Documentation of a confirmed diagnosis with mutation of alpha-galactosidase A (alpha-Gal A) gene; **AND**
 2. Documentation that member has a mutation in the gene encoding galactosidase alpha gene (GLA) resulting in a mutant protein that would respond to migalastat (Galafold) (i.e. member has an amenable GLA variant); **AND**
 3. Documentation of the member's baseline value of GL-3 inclusions per kidney interstitial capillary; **AND**
 4. Member does not have an eGFR <30 mL/minute/1.73 m² OR ESRD requiring dialysis; **AND**
 5. Member is ERT-naïve and is not a candidate for ERT (due to contraindication, etc.); **OR**
 6. Member is ERT-experienced and not able to continue ERT therapy

Renewal Evaluation

- I. Member has not been established on therapy by the use of free samples, manufacturer coupons, or otherwise; **AND**
- II. Member has received a previous prior authorization approval for this agent; **AND**
- III. Member does not have an eGFR <30 mL/minute/1.73 m² OR ESRD requiring dialysis; **AND**
- IV. Evidence of disease response with treatment as defined by a 50% reduction in GL-3 inclusions per kidney interstitial capillary compared to pre-treatment baseline; **AND**
- V. Documentation by chart notes of disease stability or improvement in clinical symptoms

Supporting Evidence

- I. Safety and efficacy of migalastat (Galafold) has not been established in pediatric patients.
- II. Eligible patients in the pivotal study (Study 011) had either never received ERT or had not received ERT for at least 6 months. Efficacy and safety of migalastat (Galafold) in combination with ERT is currently in early clinical trial stages.
- III. Migalastat is only suitable for people with specific amenable mutations. Only mutations for which migalastat produced substantial increases in enzyme activity were judged amenable. Migalastat does not work in people with non-amenable mutations. Patients with non-amenable GLA variants within the clinical study had no change from baseline in the primary endpoint of number of GL-3 inclusions per kidney interstitial capillary. Per the package insert, consultation with a clinical genetics professional is strongly recommended in cases where the amenable GLA variant is of uncertain clinical significance or may be benign (not causing Fabry disease). Refer to the table in the package insert listing specific GLA gene variants that are amenable to treatment with migalastat (Galafold) or listed within the following search tool found at: <http://www.fabrygenevariantsearch.com>. Additionally, Fabrazyme (ERT) can be used in all variants of Fabry disease for the treatment of both adults and children. Migalastat (Galafold) is only indicated in the subset of adult patients with a confirmed amenable GLA mutation.
- IV. The primary endpoint in Galafold trials was the percentage of patients who had a response ($\geq 50\%$ reduction in the number of globotriaosylceramide inclusions per kidney interstitial capillary) at 6 months. Baseline values are needed as this was the outcome measured used in clinical trials to assess treatment effect.
- V. Use of migalastat (Galafold) is not recommended in patients with severe renal impairment (eGFR <30 mL/minute/1.73 m²) or with ESRD requiring dialysis, these patients were excluded from clinical trials.
- VI. Migalastat (Galafold) has not been demonstrated in clinical trials to have a clinically meaningful benefit in patients with Fabry disease relative to placebo. While one trial concluded it has “comparable” effects on renal function relative to ERT, “comparable” was not well defined and ERT also has limited evidence for efficacy in Fabry disease. The pivotal trial for migalastat (Galafold) failed to meet its primary endpoint and its outcome measure is of unknown significance as the relationship of GL-3 inclusion reduction to specific clinical manifestations of Fabry disease has not been established. Though ERT therapy also assessed GL-3 inclusion reduction and provides low quality evidence, Fabrazyme is not specific to amendable variants and can be used in all variants of Fabry disease for the treatment of both adults and children.

References

1. Galafold [Prescribing Information]. Cranbury, NJ: Amicus Therapeutics; August 2018.
2. UpToDate, Inc. Fabry disease: Clinical features and diagnosis. UpToDate [Online Database]. Waltham, MA. Last updated July 13, 2018. Available from: <http://uptodate.com/home/index.html>. Accessed September 25, 2018.
3. UpToDate, Inc. Fabry disease: Treatment. UpToDate [Online Database]. Waltham, MA. Last updated August 8, 2017. Available from: <http://uptodate.com/home/index.html>. Accessed September 25, 2018.
4. NORD (National Organization for Rare Disorders). Fabry Disease. Available from: <https://rarediseases.org/rare-diseases/fabry-disease/>. Accessed September 25, 2018.
5. Ortiz A, Germain DP, Desnick RJ et al. Fabry disease revisited: Management and treatment recommendations for adult patients. *Mol Genet Metab*. 2018;123:416-27.
6. Eng CM, Germain DP, Banikazemi M et al. Fabry disease: Guidelines for the evaluation and management of multi-organ system involvement. *Genet Med*. 2006;8:539-48.
7. ClinicalTrials.gov. Study of the Effects of Oral AT1001 (Migalastat Hydrochloride) in Patients With Fabry Disease. Available from: <https://clinicaltrials.gov/ct2/show/NCT00925301>. Accessed September 26, 2018.
8. Germain DP, Hughes DA, Nicholls K, et al. Treatment of Fabry's Disease with the Pharmacologic Chaperone Migalastat. *N Engl J Med*. 2016;375(6):545-55.
9. Hughes DA, Nicholls K, Shankar SP, et al. Oral pharmacological chaperone migalastat compared with enzyme replacement therapy in Fabry disease: 18-month results from the randomised phase III ATTRACT study. *J Med Genet*. 2017;54(4):288-296.

Policy Implementation/Update:

Date Created	September 2018
Date Effective	November 2018
Last Updated	November 2019
Last Reviewed	09/2019

Action and Summary of Changes	Date
Specified mutation needed to have a genetically confirmed diagnosis. Added requirement for agent to be prescribed by or in consultation with an endocrinologist or a specialist in genetics.	11/2019

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP135

Description

Miglustat (Zavesca, Opfolda, Yargesa) and eliglustat (Cerdelga) are orally administered glucosylceramide synthase inhibitors.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
miglustat (generic) miglustat (Zavesca) miglustat (Yargesa)	Mild to moderate type 1 Gaucher disease for whom enzyme replacement therapy is not a therapeutic option	100 mg capsules	90 capsules/30 days
	Niemann-Pick disease type C (NPC)*		180 capsules/30 days
miglustat (Opfolda)	Late-onset Pompe disease (lysosomal acid alpha-glucosidase [GAA] deficiency) weighing ≥40 kg and who are not improving on their current enzyme replacement therapy (ERT)	65 mg capsules	8 capsules/28 days
	Niemann-Pick disease type C (NPC)*		252 capsules/28 days
eliglustat (Cerdelga)	Type 1 Gaucher disease; CYP2D6 extensive metabolizers (EMs) or intermediate metabolizers (IMs)	84 mg capsules	56 capsules/28 days
	Type 1 Gaucher disease; CYP2D6 poor metabolizers (PMs)		28 capsules/28 days

*Off-label use; See appendix below for dosing recommendations

Initial Evaluation

- Miglustat (generic, Zavesca, or Yargesa) or eliglustat (Cerdelga)** may be considered medically necessary when the following criteria are met:
 - Member is 18 years of age or older; **AND**

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- B. Medication is prescribed by, or in consultation with, a provider that specializes in the treatment of Gaucher disease (e.g., endocrinologist, geneticist, hematologist, etc.); **AND**
- C. Will not be used in combination with other medications used to treat type 1 Gaucher disease [e.g., imiglucerase (Cerezyme), taliglucerase (ElELYso), velaglucerase (Vpriv), other agents listed in this policy, etc.]; **AND**
- D. A diagnosis of **type 1 Gaucher disease** when the following are met:
 - 1. Diagnosis is confirmed by **one** of the following:
 - i. Deficiency of glucocerebrosidase (acid β -glucosidase) enzyme activity in peripheral blood leukocytes or cultured fibroblasts; **OR**
 - ii. Genetic testing confirming mutation in glucocerebrosidase (*GBA*) gene; **AND**
 - 2. The request is for generic miglustat or brand miglustat (Zavesca) or branded generic miglustat (Yargesa); **AND**
 - i. Treatment with one enzyme replacement therapy (ERT) [e.g., imiglucerase (Cerezyme), taliglucerase (ElELYso), velaglucerase (Vpriv)] has been ineffective, contraindicated, or not tolerated; **AND**
 - ii. If the request is for brand miglustat (Zavesca), the member has an intolerance or contraindication to generic miglustat*; **OR**
 - 3. The request is for eliglustat (Cerdelga); **AND**
 - i. The member has undergone CYP2D6 genotyping by an FDA-cleared test and is classified as one of the following: [Note: eliglustat (Cerdelga) is not indicated for ultra-rapid metabolizers]
 - a. Poor Metabolizer (PM); **OR**
 - b. Intermediate Metabolizer (IM); **OR**
 - c. Extensive Metabolizer; **OR**
- E. Medication is prescribed by, or in consultation with, a provider that specializes in the treatment of Niemann-Pick disease type C (e.g., neurologist, geneticist, endocrinologist, etc.); **AND**
- F. Body surface area (BSA in m²) or height (cm) and weight (kg) is documented; **AND**
- G. A diagnosis of **Niemann-Pick disease type C** when the following are met:
 - 1. The diagnosis is established by a genetic test showing biallelic pathogenic variants in either the NPC1 gene or NPC2 gene; **OR**
 - i. Presence of a mutation in one allele AND either a positive filipin-staining or elevated cholestane triol/oxysterols (>2x the upper limit of normal); **AND**
 - 2. Member has one or more neurological symptom(s) of Niemann-Pick disease type C (e.g., loss of motor function, swallowing, and speech and cognitive impairment, etc.); **AND**
 - 3. Member can walk independently or with assistance; **AND**
 - 4. Documentation that treatment with brand Opfolda* has not been tolerated or is contraindicated.

*Please note: medications notated with an asterisk may require additional review

- II. **Miglustat (Opfolda)** may be considered medically necessary when the following criteria are met:
 - A. Member is 18 years of age or older; **AND**

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- B. Medication is prescribed by, or in consultation with, a provider that specializes in the treatment of Pompe disease (e.g., neurologist, geneticist, pulmonologist, etc.); **AND**
 - C. Medication will not be used in combination with any other enzyme replacement therapies [i.e., alglucosidase-alfa (Lumizyme), avalglucosidase-alfa (Nexviazyme)]; **AND**
 - D. A diagnosis of **late-onset Pompe disease [Acid Alpha-Glucosidase (GAA) deficiency]** when the following are met:
 - 1. Diagnosis is confirmed by one of the following:
 - i. Enzyme assay showing a deficiency of acid alpha-glucosidase (GAA) activity in the blood, skin, or muscle; **OR**
 - ii. Detection of biallelic pathogenic variants in the GAA gene by molecular genetic testing; **AND**
 - 2. Attestation member has an actual body weight of at least 40 kilograms; **AND**
 - 3. Documentation of baseline values for percent predicted forced vital capacity (FVC) and/or 6-minute walk test (6MWT); **AND**
 - 4. Treatment with enzyme replacement therapy [i.e., alglucosidase-alfa (Lumizyme), avalglucosidase-alfa (Nexviazyme) has been ineffective or not tolerated; **AND**
 - 5. Medication will be used in combination with cipaglucosidase alfa-atga (Pombiliti); **OR**
 - E. Medication is prescribed by, or in consultation with, a provider that specializes in the treatment of Niemann-Pick disease type C (e.g., neurologist, geneticist, endocrinologist, etc.); **AND**
 - F. Body surface area (BSA in m²) or height (cm) and weight (kg) is documented; **AND**
 - G. A diagnosis of **Niemann-Pick disease type C** when the following are met:
 - 1. The diagnosis is established by a genetic test showing biallelic pathogenic variants in either the NPC1 gene or NPC2 gene; **OR**
 - i. Presence of a mutation in one allele AND either a positive filipin-staining or elevated cholestane triol/oxysterols (>2x the upper limit of normal); **AND**
 - 2. Member has one or more neurological symptom(s) of Niemann-Pick disease type C (e.g., loss of motor function, swallowing, and speech and cognitive impairment, etc.); **AND**
 - H. Member can walk independently or with assistance
- III. Miglustat (Zavesca, Opfolda, Yergesa), and/or eliglustat (Cerdelga) are considered investigational when used for all other conditions, including but not limited to:
- A. Type 3 Gaucher disease
 - B. Gangliosidases (GM1 and GM2)
 - C. Cystic Fibrosis
 - D. Infantile Pompe Disease
 - E. HIV Infection
 - F. Tay-Sachs Disease
 - G. Sandhoff 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**
 - A. For a diagnosis of type 1 Gaucher disease:
 1. Miglustat (Zavesca) or eliglustat (Cerdelga) will not be used in combination with other medications used for the treatment of type 1 Gaucher disease (i.e. will be used as monotherapy); **AND**
 2. Member has exhibited improvement or stability of disease manifestations [e.g., improvements in mean liver volume and/or spleen volumes, changes in hemoglobin levels and platelet count, etc.] and/or symptoms [e.g., fatigue, bleeding episodes, bruising, bone pain, etc.]; **OR**
 - B. For a diagnosis of late-onset Pompe disease [Acid Alpha-Glucosidase (GAA) deficiency; **AND**
 1. Medication will not be used in combination with any other enzyme replacement therapies [i.e., alglucosidase-alfa (Lumizyme), avalglucosidase-alfa (Nexviazyme)]; **AND**
 2. Medication will be used in combination with cipaglucosidase alfa-atga (Pombiliti); **AND**
 3. Member has exhibited improvement or stability of disease manifestations [e.g., improvements in 6MWT, FVC, etc.]
 - C. For a diagnosis of **Niemann-Pick disease type C (NPC)**:
 1. Body surface area (BSA in m²) or height (cm) and weight (kg) is documented; **AND**
 2. Member has experienced benefit from treatment defined as disease stabilization or slowed disease progression and treatment provides clinical benefit to the member (e.g., improvement in gait, sitting, stance, speech, fine motor skills, etc.)

Supporting Evidence

Gaucher Disease

- I. Miglustat (Zavesca) obtained FDA approval for treatment of type 1 Gaucher disease in 2003 based on the result of two open-label, uncontrolled studies and one randomized, open-label, active-controlled study. In the uncontrolled open-label trials, patients experienced a significant mean reduction in liver and spleen volume from baseline and non-significant change in platelet counts and hemoglobin concentration. These results were maintained or further decreased during the extension period of both trials. In the randomized, active-controlled study, patients were randomized to receive miglustat (Zavesca) alone, imiglucerase (Cerezyme) alone, or miglustat (Zavesca) in combination with imiglucerase (Cerezyme). There were no significant differences between the groups for mean absolute changes in liver and spleen volume and hemoglobin concentration. However, there was a significant reduction in platelet counts between the miglustat (Zavesca) and imiglucerase (Cerezyme) monotherapy groups. During the open-label extension period, all patients were transitioned to miglustat (Zavesca) monotherapy

and no significant changes liver volume, spleen volume, or hemoglobin concentration were observed.

- II. Eliglustat (Cerdelga) obtained FDA approval for treatment of type 1 Gaucher disease under priority review in 2014 based on the results of one randomized, double-blind, placebo-controlled study in treatment naïve patients and one randomized, open-label, active-controlled, non-inferiority study in patients transitioning from enzyme replacement therapy.
- III. A randomized, double-blind, placebo-controlled trial investigated eliglustat (Cerdelga) against placebo in type 1 Gaucher disease treatment naïve patients. The results showed a statistically significant improvement in percentage change in spleen volume and liver volume, absolute change in hemoglobin level, and percentage change in platelet count from baseline to nine months compared to placebo. During the open label extension phase, improvements in spleen and liver volume, hemoglobin level, and platelet count continued through the two-year trial duration and through four years in a separate uncontrolled trial.
- IV. A randomized, open-label, active-controlled, non-inferiority study evaluated eliglustat (Cerdelga) versus imiglucerase in patients who were previously treated with enzyme replacement therapy. The primary composite endpoint required stability in all four component domains (hemoglobin level, platelet count, liver volume and spleen volume) based on changes between baseline and 12 months according to pre-specified thresholds of change. Eliglustat (Cerdelga) met the criteria to be declared non-inferior to imiglucerase in maintaining patient stability. During the open-label extension phase, patients continued to show stability, as previously defined in the initial 12 months of the trial, at two years of treatment.
- V. Patients enrolled in the studies for miglustat (Zavesca) and eliglustat (Cerdelga) were 18 and older. The safety and/or efficacy of use in pediatric and adolescent patients has not been evaluated.
- VI. Miglustat (Zavesca) and eliglustat (Cerdelga) have largely been studied as monotherapy, with the exception of one treatment arm in a single study involving miglustat (Zavesca). Long-term safety and efficacy of either agent used in combination with enzyme replacement therapy, or other agents used to treat type 1 Gaucher disease has not been evaluated.
- VII. Gaucher disease is a rare autosomal recessive lysosomal storage disorder (LCD) that is caused by mutations in the glucocerebrosidase enzyme (*GBA*) and/or deficiency of the enzyme glucocerebrosidase. Diagnosis of Gaucher disease type 1 should be confirmed by a physician specializing in the treatment of Gaucher disease via blood tests to confirm deficiency of the glucocerebrosidase enzyme (acid β -glucosidase) in peripheral leukocytes or cultured fibroblasts or genetic testing to confirm mutation in *GBA* prior. Treatment is not necessary for all patients with Gaucher disease type 1, as some patients are asymptomatic. However, treatment is generally lifelong for symptomatic patients once treatment is initiated.
- VIII. According to recent guidelines, treatment with enzyme replacement therapy (ERT) remains first-line treatment for type 1 Gaucher disease and is delivered intravenously. Miglustat (Zavesca) is a second line oral treatment indicated when ERT is no longer accepted by the patient or cannot be tolerated. Eliglustat (Cerdelga) may be used as a first-line treatment alternative to ERT.
- IX. Miglustat (Zavesca) is commonly discontinued due to adverse effects including diarrhea (observed in over 85% of patients during clinical trials), weight loss (~65%), tremor and peripheral neuropathy. Eliglustat (Cerdelga) is generally better tolerated with the most common

adverse events comprising of arthralgia (45%), back pain (12%), fatigue (14%) and headache (13 to 40%).

- X. Miglustat (Zavesca) is contraindicated in women who are or may become pregnant. Providers should discuss the risks of teratogenicity when administered to women of reproductive potential.
- XI. Eliglustat (Cerdelga) was found to be heavily affected by a patient's CYP2D6 metabolizer status and therefore requires CYP2D6 genotyping before prescribing. Recommended dosing differs between poor metabolizers and intermediate/extensive metabolizers. Eliglustat (Cerdelga) is not recommended for ultra-rapid metabolizers due to difficulty obtaining reliable blood levels of the drug. Concurrent use of strong CYP2D6 inhibitors (e.g., bupropion, fluoxetine, paroxetine, quinidine, etc.) is not recommended and these agents should be discontinued prior to initiating therapy with eliglustat (Cerdelga).

Late-onset Pompe Disease

- I. Pompe disease (acid alpha-glucosidase deficiency) is characterized by the accumulation of glycogen within the lysosomes of all tissues. The defect in the lysosomal GAA enzyme affects lysosomal-mediated degradation of glycogenesis. Therapies for Pompe disease aim to mimic the GAA enzyme [i.e., enzyme replacement therapy (ERT)].
- II. Pompe disease manifests in one of two forms: infantile-onset disease, also known as classic disease which presents within the first few months of life, or late-onset disease which can present at any age. The course of late-onset disease is variable and progresses differently for each individual patient ranging from asymptomatic to severe progressive myopathy. In late-onset Pompe disease, the primary clinical finding is skeletal myopathy, with a more protracted course leading to respiratory failure. Adults may also progress with progressive, proximal weakness in a limb-girdle distribution which impacts the ability to walk. This weakness can affect the diaphragm leading to respiratory insufficiency early in the course of disease. In untreated patients with late-onset disease, the estimated five-year survival rate from the time of diagnosis was 95 percent and dropped to 40 percent at 30 years post-diagnosis.
- III. GAA deficiency can be confirmed via enzyme assay from the blood, skin, or muscle. Additionally, pathogenic variants of the GAA gene can be identified via molecular genetic testing. The late-onset form of GAA deficiency should be suspected in children and adults with progressive proximal weakness in a limb-girdle distribution. Additionally, the forced vital capacity (FVC) on pulmonary function testing typically is reduced substantially in adults. GAA enzyme activity can be measured in white blood cells or dried blood spots. Though gene sequencing is the preferred test to confirm the diagnosis since it is routinely available, is less invasive, may provide genotype-phenotype information, and may help predict cross-reactive immunologic material (CRIM) status (amount of residual endogenous GAA production) in some cases. The finding of two pathogenic variants in trans in the GAA gene is considered confirmatory.
- IV. Miglustat (Opfolda) in combination with cipaglucosidase alfa-atga (Pombiliti) was FDA approved in 2023 for the treatment of adults living with late-onset Pompe disease (LOPD) weighing ≥ 40 kg and who are not improving on their current enzyme replacement therapy (ERT). The combination has not been approved for use as a front-line ERT. Miglustat (Opfolda) is to be administered approximately one hour before the intravenous (IV) administration of cipaglucosidase alfa-atga (Pombiliti). As cipaglucosidase alfa-atga (Pombiliti) is an IV infusion it is coverable under the medical benefit.

- V. The combination acts together by joint mechanisms. Cipaglucosidase alfa-atga (Pombiliti) is a recombinant human GAA enzyme (rhGAA) designed for increased uptake into muscle cells. Once in the cell, cipaglucosidase alfa-atga (Pombiliti) can be properly processed into its most active and mature form to break down glycogen. Miglustat (Opfolda) is an enzyme stabilizer designed to stabilize the enzyme in the blood. Miglustat (Opfolda) itself is not an ERT, its use as an enzyme stabilizer has not been studied in combination with other ERT therapies [i.e., alglucosidase-alfa (Lumizyme), avalglucosidase-alfa (Nexviazyme)].
- VI. Cipaglucosidase alfa-atga (Pombiliti) and miglustat (Opfolda) are not FDA approved for the treatment of those under the age of 18 or for those less than 40 kilograms. Given the complexities of the treatment of Pompe disease treatment under the care of a specialist is required (e.g., neurologist, geneticist, pulmonologist, etc.).
- VII. Miglustat (Opfolda) in combination with cipaglucosidase alfa-atga (Pombiliti) was approved based on the result of a phase III, randomized, double-blind, parallel-group trial. Miglustat (Opfolda) in combination with cipaglucosidase alfa-atga (Pombiliti) was studied against alglucosidase-alfa plus placebo. Both regimens were administered in blinded dosage forms every two weeks. Both ERT-experienced and ERT-naïve patients were included. All patients were required to have a sitting forced vital capacity (FVC) of at least 30% of the predicted value for healthy adults and to have performed two valid 6-min walk tests (both 6-min walk test screening values had to be ≥ 75 m and $\leq 90\%$ of the predicted value for healthy adults).
- VIII. In the overall population, at week 52, mean change from baseline in 6MWD was 20.8 m (SE 4.6) in the cipaglucosidase alfa (Pombiliti) plus miglustat (Opfolda) group versus 7.2 m (6.6) in the alglucosidase alfa plus placebo group using last observation carried forward (between-group difference 13.6 m [95% CI -2.8 to 29.9]); however, the difference did not reach statistical significance (trial was powered for superiority). The relationship of this improvement in 6MTD is only an indirect measure as compared to other marketed products as the result was not statistically significant. The change from baseline at week 52 for FVC was measured as -0.9% in the treatment group as compared to -4.0% in the comparator group. While there are numerical differences between the treatment groups, statistical analyses of secondary endpoints were not performed as the primary endpoint did not achieve statistical significance. As such, numerical comparisons may be made, but the applicability of these results should be used with caution.
- IX. Twelve serious adverse events occurred in eight patients in the cipaglucosidase alfa plus miglustat group; only one event (anaphylaxis) was deemed related to study drug. One serious adverse event (stroke) occurred in the alglucosidase alfa plus placebo group, which was deemed unrelated to study drug. Common adverse effects included fall (29% vs 39%), headache (24% vs 24%), nasopharyngitis (22% vs 8%), myalgia (16% vs 13%), and arthralgia (15% vs 13%) in the cipaglucosidase alfa (Pombiliti) + miglustat (Opfolda) and alglucosidase alfa + placebo groups respectively.

Niemann-Pick disease type C (NPC)

- X. Niemann-Pick disease type C (NPC) is a rare, inherited lysosomal storage disorder characterized by the abnormal accumulation of cholesterol and other lipids in the cells. These genetic mutations impair the intracellular trafficking of lipids, leading to progressive neurological and hepatic dysfunction. Biomarker profile genetic testing identifying two alleles with known disease-causing mutations in either NPC1 or NPC2 gene confirms the diagnosis of NPC, and is the most reliable way to confirm the diagnosis of NPC. As a neurodegenerative disease with a

very heterogeneous presentation, symptoms typically appear in childhood and can include developmental delay, ataxia, seizures, and progressive liver enlargement, with later stages often involving cognitive decline, motor impairment, and difficulty swallowing. The age of onset of neurological symptoms predicts the severity of the disease and determines life expectancy. The prevalence of NPC is estimated to be approximately 1 in 100,000 to 150,000 live births, and it is estimated that there are 900 people in the United States with NPC. The spectrum of NPC ranges from a neonatal rapidly progressive fatal disorder to an adult-onset chronic neurodegenerative disease. The late-infantile and juvenile-onset forms account for the majority of NPC cases. Across all phenotypes, the median age of death is 13 years most often due to respiratory failure.

- XI. Therapeutic management of NPC primarily focuses on symptom management and slowing disease progression, as there is no cure. Supportive therapies, such as physical and occupational therapy, anti-seizure medications, and interventions to manage liver complications, are often recommended to address specific symptoms. Early diagnosis and intervention are crucial for improving the quality of life and prolonging survival, but the overall prognosis remains poor, particularly in later stages of the disease. Regular monitoring and a multidisciplinary care approach are essential to optimize treatment and manage complications.
- XII. Miglustat has been approved in the European Union, Canada, and Japan and is considered a standard of care for treating progressive neurological complications in NPC. Niemann-Pick Type C Guidelines Working Group and the International Niemann-Pick Disease Alliance 2018 consensus clinical management guidelines for Niemann-Pick disease type C, recommend miglustat (Yargesa, Zavesca, Opfolda), as an effective and recommended treatment option in the management of existing neurologic manifestations of NPC in children and adults who exhibit symptoms of neurological decline (Strength of recommendation: 2; Level of evidence: C). Data from a randomized, controlled trial and a retrospective, observational cohort study support the use of miglustat in the treatment of NPC disease in adults and children 12 years and older. Clinical evidence suggests that miglustat can help slow the progression of the disease, particularly in patients with moderate symptoms or in the early stages of the disease, though it does not cure NPC or reverse damage. The drug may be beneficial in delaying neurological deterioration, with effects noted on motor and cognitive functions. Administered orally, miglustat's dosage depends on the patient's age and weight, with treatment often beginning in early childhood for those with signs of neurological involvement. However, common side effects, including gastrointestinal issues such as diarrhea, nausea, and weight loss require careful monitoring. Dose adjustments are often necessary to manage these side effects. Despite miglustat's position as a standard of care, there has been no significant change in the survival of patients with NPC.
- XIII. From the 2018 International NPC guidelines, "miglustat therapy is not appropriate for patients who have profound neurological disease, which, in the opinion of the attending physician, would make it difficult to assess for any improvements with therapy. Such symptoms may include but are not limited to:
 - a. Profound dementia resulting in the need for 24 h care
 - b. Inability to ambulate without a wheelchair
 - c. Complete lack of verbal communication
 - d. Swallowing difficulties profound enough to require tube feeding through a percutaneous gastrostomy..."

Additionally, the guidelines do not recommend miglustat therapy in the following situations: patients who are pre-symptomatic or only have spleen/liver enlargement, patients with another

life-threatening illness with estimated life span less than 1 year (Strength of recommendation: 2; Level of evidence: C).

- XIV. As of September 2014, there are two FDA-approved therapies for NPC: arimoclomol (Miplyffa) and levacetylleucine (Aqneursa). Arimoclomol (Miplyffa) is an orally administered capsule that was studied and is indicated for use in combination with miglustat for the treatment of neurological manifestations of NPC in adult and pediatric patients two years of age and older and weigh ≥ 8 kg. Levacetylleucine (Aqneursa) is available as orally dosed unit packets given three times daily to treat neurological manifestations of NPC in adults and pediatric patients weighing ≥ 15 kg. Although the FDA label does not mandate the concurrent administration of miglustat with levacetylleucine (Aqneursa), it is probable that healthcare providers will choose to continue miglustat therapy when prescribing levacetylleucine (Aqneursa) as a majority of participants in the pivotal clinical trial were on concomitant miglustat (85%). There are limited data to determine the efficacy of arimoclomol (Miplyffa) without miglustat. Both trial inclusion criteria required the participants to have one or more neurological symptoms (e.g., loss of motor function, swallowing, and speech and cognitive impairment, etc.). Both treatments are backed by a single small, relatively short randomized clinical trial, with each demonstrating a statistically significant but modest difference in the primary outcome. However, even a 1- to 2-point difference on each scale can lead to a meaningful improvement in a patient's quality of life.
- XV. Arimoclomol (Miplyffa) and levacetylleucine (Aqneursa) have distinct mechanisms of action, although the exact ways in which they produce clinical effects in NPC are not fully understood. There is currently no evidence to support a synergistic effect, additive benefits, or assess safety when arimoclomol (Miplyffa) and levacetylleucine (Aqneursa) are used combination.
- XVI. There is a lack of head-to-head trials showing superior safety or efficacy comparing the different formulations of miglustat (generic, Opfolda, Yargesa, Zavesca). Given the known safety, established efficacy, and cost-effectiveness, Opfolda formulation requires to be tried and failed first. Generic miglustat, brand Yargesa and Zavesca are 6 - 8 times more costly than Opfolda, without any evidence of improved clinical efficacy or safety. Opfolda is available in 65-mg capsules, which may not allow for exact dosing (195 mg vs. 200 mg); however, given the dosing discrepancy (~2.5%), it is anticipated that the minor difference has a similar and/or negligible clinical impact.

Investigational or Not Medically Necessary Uses

- I. Miglustat (Opfolda, Yargesa, Zavesca) and/or eliglustat (Cerdelga) have not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
- A. Type 3 Gaucher disease
 - B. Gangliosidases (GM1 and GM2)
 - C. Cystic Fibrosis
 - D. Infantile Onset Pompe Disease
 - E. HIV Infection
 - F. Tay-Sachs Disease
 - G. Sandhoff Disease

Appendix

- I. While not FDA-approved, miglustat dosing is based on the doses studied in clinical trials/compendia and dose approved in the European Union for NPC. Miglustat use requires

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careful monitoring for side effects and regular treatment adjustments to optimize patient outcomes. Some forms of miglustat (Opfolda) are available in 65-mg capsules, therefore certain treatment regimens may not allow for exact dosing. *Please refer to updated clinical compendia for dosing recommendations.*

Table 1. Off-label dosing for miglustat based on clinical compendia		
Patient population	BSA	Miglustat dose
<12 years of age	BSA ≤0.47 m ²	100 mg once daily
	BSA >0.47 to 0.73 m ²	100 mg 2 times daily
	BSA >0.73 to 0.88 m ²	100 mg 3 times daily
	BSA >0.88 to 1.25 m ²	200 mg 2 times daily
	BSA >1.25 m ²	200 mg 3 times daily
>12 years of age and older	-	200 mg 3 times daily

II. $BSA (m^2) = \sqrt{\frac{\text{height (cm)} \times \text{weight (kg)}}{3600}}$

References

1. Stirnemann J, Belmatoug N, Camou F, et al. A Review of Gaucher Disease Pathophysiology, Clinical Presentation and Treatments. *Int. J. Mol. Sci.* 2017, 18, 441; doi: 10.3390/ijms18020441
2. Gary SE, Ryan E, et al. Recent advances in the diagnosis and management of Gaucher disease. *Expert Rev Endocrinol Metab.* 2018 March; 13(2):107-118. Doi:10.1080/17446651.2018.1445524.
3. Wang RY, Bodamer OA, et al. Lysosomal storage diseases: Diagnostic confirmation and management of presymptomatic individuals. ACMG Standards and Guidelines. *Genetics in Medicine.* 2011 May; 13(5).
4. Miglustat [Prescribing Information]. Actelion Pharmaceuticals US, Inc. South San Francisco, CA. November 2017.
5. Eliglustat [Prescribing Information]. Genzyme Ireland, Ltd.: Waterford, Ireland. August 2018.
6. Safety and efficacy of cipaglucosidase alfa plus miglustat versus alglucosidase alfa plus placebo in late-onset Pompe disease (PROPEL): an international, randomised, double-blind, parallel-group, phase 3 trial Schoser B, Roberts M, Byrne BJ, et al. Safety and efficacy of cipaglucosidase alfa plus miglustat versus alglucosidase alfa plus placebo in late-onset Pompe disease (PROPEL): an international, randomised, double-blind, parallel-group, phase 3 trial [published correction appears in *Lancet Neurol.* 2023 Oct;22(10):e11]. *Lancet Neurol.* 2021;20(12):1027-1037.
7. Schoser B, Kishnani PS, Bratkovic D, et al. 104-week efficacy and safety of cipaglucosidase alfa plus miglustat in adults with late-onset Pompe disease: a phase III open-label extension study (ATB200-07). *J Neurol.* 2024;271(5):2810-2823.
8. Opfolda [Prescribing Information]. Amicus Therapeutics US, LLC. Philadelphia, PA. September 2023.
9. Pombiliti [Prescribing Information]. Amicus Therapeutics US, LLC. Philadelphia, PA. September 2023.
10. Miglustat [Prescribing Information]. Actelion Pharmaceuticals US, Inc. South San Francisco, CA. November 2017.
11. Opfolda [Prescribing Information]. Amicus Therapeutics US, LLC. Philadelphia, PA. September 2023.
12. Geberhiwot T, Moro A, Dardis A, et al. Consensus clinical management guidelines for Niemann-Pick disease type C. *Orphanet J Rare Dis.* 2018;13(1):50.
13. Burton BK, et al. Estimating the prevalence of Niemann-Pick disease type C (NPC) in the United States. *Mol Genet Metab.* 2021;134(1-2):182-187.
14. Cortina-Borja M, et al. Annual severity increment score as a tool for stratifying patients with Niemann-Pick disease type C and for recruitment to clinical trials. *Orphanet J Rare Dis.* 2018;13(1):143.
15. Mengel E, et al. Efficacy and safety of arimoclomol in Niemann-Pick disease type C: results from a double-blind, randomized, placebo-controlled, multinational phase 2/3 trial of a novel treatment. *J Inheri Metab Dis.* 2021;44(6):1463-1480.
16. Patterson MC, et al. Validation of the 5-domain Niemann-Pick type C clinical severity scale. *Orphanet J Rare Dis.* 2021;16(79):1-9.
17. Bremova-Ertl T, Ramaswami U, Brands M, et al. Trial of N -Acetyl- I -Leucine in Niemann-Pick Disease Type C. *N Engl J Med.* 2024;390(5):421-431.
18. Martakis K, et al. Long-term findings of N-acetyl-L-leucine for Niemann-Pick disease type C. *Neuropediatrics.* 2024;55(S01):S1-S25.

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
arimoclomol (Miplyffa™) and levacetylleucine (Aqneursa™) Policy	Niemann-Pick disease type C

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated criteria to include a path to coverage for miglustat in Niemann Pick type C (NPC). Removed NPC from Experimental and Investigational section. Updated appendix, supporting evidence, references, and related policies.	02/2025
Updated criteria to include Miglustat (Opfolda) in combination with cipaglucosidase alfa-atga (Pombiliti) for the treatment of late-onset Pompe disease. Updated E/I criteria from Pompe disease to include the infantile-onset subtype of Pompe disease specifically. Updated formatting of the supporting evidence.	06/2024
Transitioned criteria to new policy format and combined previous miglustat and eliglustat criteria into one policy and added the following requirements: age 18 and older, prescribed by or in consultation with specialist, used as monotherapy and diagnosis confirmed by genetic and/or blood testing	11/2020
Miglustat (Zavesca) criteria created	05/2018
Eliglustat (Cerdelga) criteria created	11/2014

Policy Type: QE

Pharmacy Coverage Policy: UMP160

Description

Migraine abortive therapies, or acute treatments, include triptans, CGRP antagonists, and lasmiditan (Reyvow) which is a selective serotonin agonist.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Quantity Limit	Quantity Exception
almotriptan	6.25 mg tablet	9 tablets/30 days	20 tablets/30 days
	12.5 mg tablet	12 tablets/30 days	20 tablets/30 days
almotriptan (Axert)	12.5 mg tablet	12 tablets/30 days	20 tablets/30 days
eletriptan	20 mg tablet	9 tablets/30 days	20 tablets/30 days
	40 mg tablet		
eletriptan (Relpax)	20 mg tablet	9 tablets/30 days	20 tablets/30 days
	40 mg tablet		
frovatriptan	2.5 mg tablet	9 tablets/30 days	27 tablets/30 days
frovatriptan (Frova)	2.5 mg tablet	9 tablets/30 days	27 tablets/30 days
naratriptan	1 mg tablet	9 tablets/30 days	20 tablets/30 days
	2.5 mg tablet		
naratriptan (Amerge)	1 mg tablet	9 tablets/30 days	20 tablets/30 days
	2.5 mg tablet		
rizatriptan	5 mg tablet	12 tablets/30 days	30 tablets/30 days
	5 mg ODT		
	10 mg tablet		
	10 mg ODT		
rizatriptan (Maxalt)	5 mg tablet	12 tablets/30 days	30 tablets/30 days
	10 mg tablet		
rizatriptan (Maxalt-MLT)	10 mg tablet	12 tablets/30 days	30 tablets/30 days
sumatriptan (oral)	25 mg tablet	9 tablets/30 days	20 tablets/30 days
	50 mg tablet		
	100 mg tablet		
sumatriptan (Imitrex) (oral)	25 mg tablet	9 tablets/30 days	20 tablets/30 days
	50 mg tablet		
	100 mg tablet		
sumatriptan/naproxen (oral)	85-500 mg tablet	9 tablets/30 days	20 tablets/30 days
sumatriptan/	85-500 mg tablet	9 tablets/30 days	20 tablets/30 days

naproxen (Treximet) (oral)			
sumatriptan (nasal)	5 mg spray	6 doses (1 box)/30 days	18 doses (3 boxes)/30 days
	20 mg spray		
sumatriptan (Imitrex) (nasal)	5 mg spray	6 doses (1 box)/30 days	18 doses (3 boxes)/30 days
	20 mg spray		
sumatriptan (Onzetra Xsail) (nasal)	11 mg powder	16 nosepieces (1 kit/8 doses)/30 days	32 nosepieces (2 kits/16 doses)/30 days
sumatriptan (Tosymra) (nasal)	10 mg spray	6 doses (1 box)/30 days	18 doses (3 boxes)/30 days
sumatriptan (SQ)	4 mg/0.5 mL	4 mL (4 kits, 8 doses)/30 days	8 mL (8 kits, 16 doses)/30 days
	6 mg/0.5mL		
sumatriptan (Imitrex) (SQ)	4 mg/0.5 mL Kit	4 mL (4 kits, 8 doses)/30 days	8 mL (8 kits, 16 doses)/30 days
	6 mg/0.5 mL solution		
sumatriptan (Imitrex Statdose) (SQ)	4 mg/0.5 mL solution	4 mL (4 kits, 8 doses)/30 days	8 mL (8 kits, 16 doses)/30 days
	6 mg/0.5 mL refill		
	6mg/0.5 ML system		
sumatriptan (Zembrace Symtouch) (SQ)	3 mg/0.5 mL solution	4 mL (4 kits, 8 doses)/30 days	8 mL (8 kits, 16 doses)/30 days
zolmitriptan (oral)	2.5 mg tablet	9 tablets/30 days	20 tablets/30 days
	5 mg tablet		
	2.5 mg ODT		
	5 mg ODT		
zolmitriptan (Zomig/ZMT) (oral)	2.5 mg tablet	9 tablets/30 days	20 tablets/30 days
	5mg tablet		
	2.5 mg ODT		
	5 mg ODT		
zolmitriptan (Zomig) (nasal)	2.5 mg spray	6 doses/30 days	18 doses (3 boxes)/30 days
	5 mg spray		
lasmiditan (Reyvow)	50 mg tablet	4 tablets/30 days	8 tablets/30 days
	100 mg tablet	8 tablets/30 days	16 tablets/30 days
ubrogepant (Ubrelvy)	50 mg tablet	10 tablets/30 days	16 tablets/30 days
	100 mg tablet	10 tablets/30 days	32 tablets/30 days
celecoxib (Elyxyb)	120 MG/4.8ML oral solution	43.2 mL (9 doses)/30 days	56.4 mL (18 doses)/30 days
diclofenac potassium (Cambia)	50 mg packet	9 packets/30 days	18 packets/30 days
zavegepant (Zavzpret) (nasal)	10mg spray	6 doses/30 days	12 doses/30 days
ergotamine (Ergomar) (SL tab)	2 mg sublingual tablet	12 tablets/30 days	20 tablets/30 days

Initial Evaluation

- I. A quantity exception may be considered medically necessary when the following criteria below are met:
 - A. Member has tried and failed prophylactic therapy with at least one agent listed in EACH of the three groups (these specific agents required). Please note, if a group is contraindicated, a trial and failure of three remaining agent is required:
 1. Group 1: propranolol, metoprolol, atenolol, timolol, nadolol
 2. Group 2: amitriptyline, venlafaxine
 3. Group 3: topiramate, sodium valproate, divalproex sodium; **AND**
 - B. The member has tried each of the prophylactic therapies for at least three months, or did not tolerate therapy with an adequate trial; **AND**
 - C. Provider attestation that medication overuse headache has been ruled out as the cause or contributor to the member's migraines.
- II. Triptans, lasmiditan (Reyvow), and ubrogepant (Ubrelevy) are considered investigational when used for all other conditions, including but not limited to:
 - A. Migraine prophylaxis

Renewal Evaluation

- I. Member has exhibited improvement or stability of disease symptoms (e.g., reduction in migraine symptom severity, duration, etc.) with the quantity previously allowed; **AND**
- II. Provider attestation that the member is being monitored for medication overuse headache and the requested therapy is not causing or adding to medication overuse headache; **AND**
- III. Provider attestation that the member is still in need of the quantity being requested and the member stockpiling is not occurring.

Supporting Evidence

- I. This policy aims to ensure appropriate use of prescription abortive migraine therapies, limit overuse, occurrence of rebound headache, and direct members to migraine prevention therapy when appropriate.
- II. Triptans have an established safety and efficacy profile for the abortive treatment of migraine; however, overuse of these therapies may result in exacerbation of migraine (i.e., medication overuse headache). Medication overuse headache (MOH) may occur with other therapies for abortive migraine treatment including, but not limited to: acetaminophen, NSAIDs, opioids, and ergot derivatives. After lifestyle modifications, non-pharmacologic therapies, and avoidance of triggers have been employed, pharmacologic therapy may be necessary. Triptans are the mainstay of therapy and are recommended as first-line treatment by governing bodies and treatment guidelines such as American Academy of Neurology, American Family Physician, and American Headache Society. Avoidance of MOH may be employed by using triptans less than two days per week on average, and package inserts for many triptan therapies recommend using less than 10 days per month. Prior to use of this frequency of triptans, prophylactic therapy for prevention of migraine may be warranted. Triptans are not indicated for the continual prophylactic treatment of migraine.

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- III. As of March 2020, MOH had not been noted for CGRP-antagonists or ubrogepant (Ubrelevy); however, long term safety data in treating more than 15 or eight migraines per month, respectively, has not been evaluated. These therapies are not indicated for prevention of migraine. For ubrogepant (Ubrelevy) the daily maximum dose is 200 mg.
- IV. Lasmiditan (Reyvow) has warnings for MOH in the prescribing information. The label indicates treatment of more than four migraine days per months has not been evaluated and treating 10 or more migraines per month with this or other abortive migraine therapies may contribute to worsening of migraines. The daily maximum dose is 200 mg per day.
- V. The agents listed in the policy are recommended by guidelines with Level A and B recommendations (i.e., efficacious or probably efficacious). There is no available evidence, or evidence to suggest against, use of any other agent not in the list above (e.g., gabapentin, nortriptyline, calcium channel blockers, SSRIs). These agents should not be considered for an adequate trial of prophylactic therapy given the negative or no evidence.
- VI. Guidelines label a “treatment success” with prophylactic therapy as a 50% reduction in migraine after three months. Additionally, some agents take one-to-three months to show efficacy. If the prophylactic therapy has not been trialed for three months, the trial is not considered adequate for prophylactic efficacy; however, many migraine sufferers are unable to tolerate the recommended prophylactic therapies.
- VII. The quantity limits are based on maximum daily dose, as recommended per the FDA, as well as treating with migraine therapies ten or less days per month, package size considerations as well as safety of therapies contained in this policy.

Investigational or Not Medically Necessary Uses

- I. Triptans, lasmiditan (Reyvow), and ubrogepant (Ubrelevy) have not been FDA-approved, or sufficiently studied for safety and efficacy for migraine prophylaxis.

References

1. Oregon Health & Sciences University (OHSU). Drug Class Review on Triptans Final Report Update 3. November 2005
2. Eras M., Gursoy AE., Prophylactic treatment of migraine. *Noro Psikiyatr Ars.* 2013;50(1):30-35.
3. Miller S. The acute and preventative treatment of episodic migraine. *Ann Indian Acad Neurol.* 2012;15(1):33-39.
4. Modi S., Lowder D. Medications for migraine prophylaxis. *Am Fam Physician.* 2006;73(1):72-78.
5. Silberstein S., Tfelt-Hansen P., Dodick DW., et al. Guidelines for controlled trials of prophylactic treatment of chronic migraine in adults. *Cephalalgia.* 2008;28:484-495.
6. Lenz R., Bonafede M., Maiese B., et al. Prophylaxis and acute medication treatment patters in migraine patient initiating migraine prophylactic therapy. *Amer Acad Neurol.* 2016;86(1):206.
7. Marmura MJ, Silberstein SD, Schwedt TJ. The acute treatment of migraine in adults: the American Headache Society evidence assessment of migraine pharmacotherapies. *Headache.* 2015;55(1):3-20.
8. Gilmore G., Geffen D., Michael M., et al. Treatment of acute migraine headaches. *Am Fam Physician.* 2011;83(3):271-280.
9. Ubrelevy [Prescribing Information]. Allergan. Madison, NJ. 2019.
10. Reyvow [Prescribing Information]. Eli Lilly. Indianapolis, IN. 2020.

Policy Implementation/Update:

Action and Summary of Changes	Date
Added ergotamine (Ergomar) (SL tab) to the policy	02/2025
Updated Ubrelevy 50mg and 100mg quantity limit to 10 per 30 days	07/2024
Updated wording on sumatriptan (Onzetra Xsail) (nasal) quantity limit for clarity	01/2024

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Added zavegepant (Zavzpret) nasal spray and respective quantity limits	06/2023
Added in celecoxib (Elyxyb) oral solution and Cambia oral packets and respective quantity limits	12/2021
Removed Nurtec from current policy as this was moved to Aimovig, Emgality, Ajovy/CGRP policy instead	04/2021
Corrected quantity limit for Nurtec to reflect manufacturer guidance and allowance of 8/30 or 16/30	07/2020
New FDA-approved migraine therapies added to policy: lasmiditan (Reyvow), ubrogepant (Ubrelvy), rimegepant (Nurtec ODT).	04/2020
Prior authorization criteria transitioned to policy format. Addition of requirement to rule out medication overuse headache, inclusion of new agents and removal of obsolete products.	12/2019
Update to delete step therapy questions to align with current processes, created tables for QLL, changed question on prophylactic therapy options to fit with current evidence and guidelines, added duration of therapy question to ensure appropriate trial of prophylactic therapy, updated agent chart.	05/2018
Updated with clinical note regarding pediatric strength of Treximet.	10/2016
Updated with Onzentra Xsail.	05/2016
Reviewed and Updated: validated and updated product availability and quantity limit lists. Criteria updated to include trial of three therapeutic categories, removal of questions on daily triptan use and specialty provider.	01/2016
Previous Reviews	08/2014, 01/2013, 08/2012, 04/2012
Policy created	09/2011

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP097

Description

Miltefosine (Impavido) is an orally administered antileishmanial medication that induces apoptosis-like cell death and stops the growth of specific *Leishmania* species.

Length of Authorization

- Initial: 28 days
- Renewal: No renewal

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
miltefosine (Impavido)	50 mg capsules	Visceral leishmaniasis	30 to 44 kg: 56 capsules/28 days OR ≥ 45 kg: 84 capsules/28days
		Cutaneous leishmaniasis	
		Mucosal leishmaniasis	

Initial Evaluation

- I. Miltefosine (Impavido) may be considered medically necessary when the following criteria below are met:
 - A. Member is 12 years of age or older; **AND**
 - B. Member weighs at least 30 kg (66 lbs); **AND**
 - C. Medication is prescribed by, or in consultation with an infectious disease specialist; **AND**
 - D. A diagnosis of one of the following:
 1. Visceral leishmaniasis due to *Leishmania donovani*; **OR**
 2. Cutaneous leishmaniasis due to the following: *Leishmania braziliensis*, *Leishmania guyanensis*, or *Leishmania panamensis*; **OR**
 3. Mucosal leishmaniasis due to *Leishmania braziliensis*; **AND**
 - E. Laboratory confirmation of leishmaniasis species were identified following **ONE** of the recommended tests provided by the Centers for Disease Control and Prevention (CDC) listed here:
 1. Stained slides (using tissue from biopsy specimens, impression smears or dermal scrapings)
 2. Culture medium
 3. Polymerase chain reaction (PCR)
 4. Serologic testing (e.g., rK39 Rapid Test); **AND**
 - F. For the diagnosis of visceral leishmaniasis, treatment with liposomal amphotericin B (Ambisome) has been ineffective, contraindicated, or not tolerated.

- II. Miltefosine (Impavido) is considered not medically necessary when criteria above are not met and/or when used for:
 - A. The treatment of leishmaniasis outside of the visceral/cutaneous/mucosal settings, and not due to the species associated with visceral/cutaneous/mucosal leishmaniasis.

Supporting Evidence

- I. Miltefosine (Impavido) is FDA-approved in the adolescents and adults ≥ 12 years and older weighing ≥ 30 kg (66lbs).
- II. For the treatment of visceral leishmaniasis, the safety and efficacy was studied in one randomized, open-label, active-controlled (amphotericin B) trial in Bihar, India. The final cure rates for miltefosine (Impavido) and amphotericin B were 94% and 97%, respectively. Final cure was defined as initial cure at end of therapy plus absence of signs and symptoms of visceral leishmaniasis at six months follow up.
- III. For the treatment of cutaneous leishmaniasis, the safety and efficacy was studied in a placebo controlled study in Colombia, Guatemala and Brazil. The finally cure rates at 95% CI with P-value <0.0001 were reported:
 - A. Colombia: 82% miltefosine (Impavido) vs 30% placebo
 - B. Guatemala: 48% miltefosine (Impavido) vs 20% placebo
 - C. Brazil: 76.3% miltefosine (Impavido), placebo was not reported.
- IV. For the treatment of mucosal leishmaniasis, the safety and efficacy was studied in a single-arm study in Bolivia that included 79 patients. At the end of therapy, reported at 12 months, 49 patients (62%) had complete resolution of edema, erythema, infiltration, and erosion from the involved mucosal sites.
- V. The CDC has specific guidelines for leishmaniasis confirmation test. They can be found here: https://www.cdc.gov/parasites/leishmaniasis/resources/pdf/cdc_diagnosis_guide_leishmaniasis_2016.pdf.

Investigational or Not Medically Necessary Uses

- I. The treatment of leishmaniasis outside of the visceral/cutaneous/mucosal settings, and not due to the species associated with visceral/cutaneous/mucosal leishmaniasis.
 - A. There is limited evidence to suggest the safety and efficacy of miltefosine (Impavido) outside of the FDA approved leishmaniasis settings and the specific species accordingly.

References

1. Impavido [Prescribing Information]. Wilmington, DE: Paladin Therapeutics, Inc. March 2014.
2. Centers for Disease Control and Prevention. Diagnosis and Treatment of Leishmaniasis: Clinical Practice Guidelines by the Infectious Disease Society (IDSA) and the American Society of Tropical Medicine and Hygiene (ASTMH). October 2018. Available at: https://www.cdc.gov/parasites/leishmaniasis/health_professionals/index.html#dx

Policy Implementation/Update:

Date Created	April 2016
Date Effective	August 2016
Last Updated	October 2019
Last Reviewed	4/2016, 10/2019

Action and Summary of Changes	Date
Transitioned criteria into policy with the following additions: supporting evidence, investigational section and CDC diagnostic recommendations.	10/2019

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP255

Description

Mitapivat (Pyrukynd) is an orally administered pyruvate kinase activator.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
mitapivat (Pyrukynd)	Hemolytic anemia in patients with pyruvate kinase deficiency	5 mg tablets	56 tablets/28 days
		20 mg tablets	
		50 mg tablets	
		5 mg tablet taper pack	7 tablets/7 days*
		20 mg and 5 mg taper pack	14 tablets/14 days*
		50 mg and 20 mg taper pack	14 tablets/14 days*

*In patients established on treatment and are discontinuing treatment, one fill of one of the taper packs will be allowed.

Initial Evaluation

- I. **Mitapivat (Pyrukynd)** 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 a hematologist; **AND**
 - C. A diagnosis of **pyruvate kinase deficiency (PKD)** when the following are met:
 1. Provider attestation to all of the following;
 - i. Diagnosis is confirmed via genetic testing (documentation of results required); **AND**
 - ii. Presence of two mutant alleles in the PKLR gene; **AND**
 - iii. At least one missense mutation (i.e., presence of two non-missense mutations does not qualify for therapy); **AND**
 - iv. Member is NOT homozygous for the R479H mutation; **AND**
 2. Hemoglobin level is less than 10 mg/dL, measured within the past three months; **AND**
 3. Documentation of baseline hemoglobin level (for renewal assessment); **AND**
 4. Member has symptoms of hemolytic anemia (e.g., fatigue, weakness, dizziness, jaundice) that negatively impact quality of life; **AND**
 5. The member has been regularly transfused or transfusion-dependent for at least 12 months (e.g., five or more blood transfusions over the past year); **OR**

- i. The member is unable to tolerate blood transfusions and/or is not a candidate for blood transfusions. Documentation of rationale required.
- II. Mitapivat (Pyrukynd) is considered not medically necessary when criteria above are not met and/or when used for:
 - A. Patients with pyruvate kinase deficiency that have two non-missense mutations or are homozygous for R479H mutation.
 - B. Hemolytic anemia in patients with PKD that do not have symptoms or symptoms severe enough to impact quality of life.
- III. Mitapivat (Pyrukynd) is considered investigational when used for all other conditions, including but not limited to:
 - A. Pediatric patients with PKD
 - B. Sickle cell disease
 - C. Thalassemia

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 hemoglobin level (measured within the past three months) has increased compared to baseline; **AND**
- IV. Documentation that the member's symptoms have improved compared to baseline.

Supporting Evidence

- I. Mitapivat (Pyrukynd) is a pyruvate kinase (PK) activator for hemolytic anemia in adults with PKD. Safety and efficacy have not been established in pediatrics, but ongoing clinical trials are evaluating. Evidence for use is limited to a small adult-only population; it is unknown if the results are applicable to pediatrics. Pediatrics utilizing mitapivat (Pyrukynd) are best monitored under a clinical trial setting until therapy is FDA-approved for patients under the age of 18.
- II. Individuals with PKD have two PKLR gene mutations, either homozygous for a single mutation or compound heterozygotes for two different mutations. Individuals with one mutation are generally not affected by PKD symptoms and do not require treatment. Mitapivat (Pyrukynd) has not been evaluated and has unknown clinical value in this population.
- III. Diagnostics for PKD include biochemical measurement of red blood cell PK activity, and genetic testing. PKD is rare and may be misdiagnosed. Additionally, in clinical trials patients homozygous for R479H or those with two non-missense mutations did not respond to treatment. Thus, genetic testing is required to determine appropriate diagnosis with responsive mutations prior to coverage consideration. Agios Pharmaceuticals Inc. offers a complimentary genetic test.

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Biochemical testing (e.g., PK activity, etc.) is insufficient to determine a diagnosis of PKD, and does not provide present mutations. Given the genetic, symptomatic, and management complexities of this condition, prescription by a specialist provider is required.

- IV. PKD management is based on symptom severity, which varies between patients even when Hb levels are comparable. When patients are experiencing symptoms that impact quality of life (QOL), supportive management/treatment may be warranted. Management strategies include:
- Blood transfusions, often coupled with iron chelation therapy to prevent iron overload.
 - Splenectomy, which may reduce transfusion burden and improve symptoms; however, is not curative. Optimal timing of splenectomy is between 5-18 years of age given risks.
 - Folic acid may be administered in those with a deficiency.
- V. The National Cancer Institute classified anemia into five grades: Grade 1 (mild): hemoglobin (Hb) of 10 g/dL to the lower limit of normal for member age and gender, Grade 2 (moderate): Hb between 8-10 g/dL, Grade 3 (severe), Grade 4 (life-threatening), and Grade 5 is death. Mitapivat (Pyrukynd) was evaluated in patients with a Hb of 10 g/dL or less (i.e., at least moderate anemia), and this is the patient population expected to have symptoms that negatively impact QOL. Unmanaged patients with Hb above 10 g/dL are near normal levels and unlikely require treatment. A Hb level measured within the past three months is required to ensure treatment is appropriate. Documentation of baseline Hb is required upon initiation to determine objective therapeutic effect upon renewal. Not all patients in clinical trials responded to treatment. Additionally, documented symptom response is required given that PKD is managed/treated on the basis of symptoms and not target Hb levels, especially as positive long-term impact on the disease has not been demonstrated for this therapy. In absence of patient-reported symptom improvement, use of mitapivat (Pyrukynd) should not be continued.
- VI. Mitapivat (Pyrukynd) was evaluated in two Phase 3 trials. Objective hematopoiesis measures and subjective patient reported outcomes (PROs) were evaluated. The Pyruvate Kinase Deficiency Diary (PKDD) and the Pyruvate Kinase Deficiency Impact assessment (PKDIA) measure daily signs of symptoms of PKD and impact on daily social and physical activities, respectively. Meaningful changes are predicted to be 5-8 points for PKDD and 6-10 points for PKDIA.
- ACTIVATE-T: Single-arm trial, over 24 weeks in regularly transfused patients (≥ 6 /year). Baseline Hb: 9.1 g/dL. Outcomes: proportion of patients with transfusion response (33% reduction in transfusion burden), transfusion-free patients, and those achieving a normal Hb. Nine patients (33%) met transfusion response, 6 (22%) became transfusion-free, and 3 (11%) achieved normal Hb levels. Although not powered or evaluated for significance, the average PKDD average score decreased by -2.4 points (baseline was 51.9), and the PKDIA score decreased by -9.1 on average (baseline 52.6).
 - ACTIVATE: An open-label, placebo-controlled trial over 12 weeks in patients not regularly transfused (≤ 4 /year). Baseline Hb was 8.5-8.6 g/dL. Outcomes: Hb response (Hb change of ≥ 1.5 g/dL), and PROs. Hb response was seen in 16 (40%) of patients on mitapivat (Pyrukynd) vs. no patients in the placebo group, and the average change in Hb was +1.7 g/dL compared to -0.1 g/dL for the placebo group, both of which were statistically and clinically significant. The PKDD score at week 24 had decreased by 5.16 points on average compared to baseline for mitapivat (Pyrukynd) which was statistically significant over placebo. The PKDIA scores reached statistical superiority over placebo but did not meet clinically relevant thresholds.

- VII. In ACTIVATE, serious adverse events (AE) occurred in 10% of patients on mitapivat (Pyrukynd), including atrial fibrillation, gastroenteritis, rib fracture, musculoskeletal pain. Common AE that occurred in at least 5% of patients and higher than placebo included decrease estrone (56%) and decreased estradiol (12%) in males only, increased urate, back pain, arthralgia, dyslipidemia, gastroenteritis, hot flush, oropharyngeal pain, hypertension, arrhythmia, breast discomfort, constipation, dry mouth and paresthesia. Around 155 patients have been treated with mitapivat (Pyrukynd) to date; thus, the full safety profile is likely not well understood.
- VIII. Transfusions may place a high burden on patients. In the ASH publication, Management of Pyruvate Kinase Deficiency in Children and Adults (Grace, Barcellini, 2020), regularly transfused patients are those that receive six or more transfusions per year, where those that are not regularly transfused are those that have received four or fewer. Mitapivat (Pyrukynd) has shown to increase Hb levels and reduce transfusion burden, likely providing clinical value in those that have a high-transfusion burden, need treatment but are unable to tolerate transfusions (e.g., previous immune or hemolytic transfusion reaction), or where risks of transfusion outweigh the benefits. Long term implications on patient-perceived burden of disease, improved survival, positive impacts on bone mineral density, prevention of iron overload, etc. have not been shown. Furthermore, very few patients in the clinical trials were able to become transfusion-free. It is likely that transfusions will need to be continued in some capacity for most patients even after starting mitapivat (Pyrukynd). Mitapivat (Pyrukynd) has questionable value over transfusions in those that could be managed with transfusions intermittently. In the not regularly transfused population, improvement in markers of hemolysis and Hb were seen; however Hb level is not strongly correlated with symptom severity and thus need for treatment. The PKDD diary assessment met the minimally important clinical change; however, PKDIA scores, which measure QOL and physical functioning, did not meet clinically meaningful thresholds. In summary, mitapivat (Pyrukynd) may be a valuable therapy in those that are not candidates for current management strategies or where transfusion-burden is high. Therapy is determined as medically necessary in those beyond the definition of not regularly transfused (i.e., those eligible are those with five or more transfusions over the past year).
- IX. In clinical trials, increases in Hb occurred rapidly in responders, with average increases in Hb by week eight of therapy. The max dose will be reached by the start of the third month; thus, a three-month initial duration of approval is sufficient to determine treatment response. Thereafter, Hb level within the past three months is required to confirm continued treatment benefit. In clinical trials not all patients responded to therapy or responded long-term. In the long-term extension trial, duration of response up to 19.5 months occurred in some patients, but many patients do not have extended duration of response. When subjective response or objective Hb response lapse, therapy should be discontinued.

Investigational or Not Medically Necessary Uses

- I. Mitapivat (Pyrukynd) is considered not medically necessary:
 - A. For patients with pyruvate kinase deficiency that have two non-missense mutations or are homozygous for R479H mutation. In a Phase 2, DRIVE-PK study of mitapivat (Pyrukynd) patients with these mutational characteristics were non-responders. Thus, the pivotal Phase 3 trials excluded these patients from enrollment.

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- B. For patients that are not experiencing symptoms severe enough to impact QOL. Decision to treat in PKD is based on symptom severity, rather than objective markers (e.g., Hb). The currently known value of mitapivat (Pyrukynd) is to improve symptoms of disease by increasing Hb. There are no data to show an impact on long-term outcomes of disease.
- II. Mitapivat (Pyrukynd) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below. Clinical trials are underway to investigate:
 - A. Pediatric patients with PKD
 - B. Sickle cell disease
 - C. Thalassemia

References

1. Grace RF, Rose C, Layton DM, et al. Safety and efficacy of mitapivat in pyruvate kinase deficiency. *New England Journal of Medicine*. 2019;381(10):933-944.
2. Pyrukynd [Prescribing Information]. Agios Pharmaceuticals Inc. Cambridge, MA. February 2022.
3. Agios Pharmaceuticals, Inc. A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Ag-348 in Not Regularly Transfused Adult Subjects with Pyruvate Kinase Deficiency. clinicaltrials.gov; 2020.
4. Agios Pharmaceuticals, Inc. An Open-Label Study to Evaluate the Efficacy and Safety of Ag-348 in Regularly Transfused Adult Subjects with Pyruvate Kinase (Pk) Deficiency. clinicaltrials.gov; 2021.
5. Grace RF, Barcellini W. Management of pyruvate kinase deficiency in children and adults. *Blood*. 2020;136(11):1241-1249.

Related Policies

There are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2022

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP287

Description

Momelotinib (Ojjaara) is an orally administered inhibitor of Janus Associated Kinase (JAK1 and JAK2) and Activin Type I receptor (ACVR1).

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
momelotinib (Ojjaara)	Intermediate or high-risk myelofibrosis with anemia	200 mg tablets	30 tablets/30 days
		150 mg tablets	
		100 mg tablets	

Initial Evaluation

- I. **Momelotinib (Ojjaara)** 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. Medication will not be used in combination with another JAK inhibitor [e.g., ruxolitinib (Jakafi), fedratinib (Inrebic), pacritinib (Vonjo)]; **AND**
 - D. A diagnosis of **myelofibrosis** (MF; including primary MF, post-polycythemia vera MF, or post-essential thrombocythemia MF) when the following are met:
 1. Member's condition is classified as intermediate (Int-1, Int-2) or high-risk myelofibrosis; **AND**
 2. Member is not a candidate for allogeneic hematopoietic cell transplant (HCT); **AND**
 3. Provider attests that the member has significant splenomegaly (increased spleen volume or size); **AND**
 4. Documentation of pre-treatment platelet counts showing that the member has a platelet count greater than or equal to 50×10^9 /L; **AND**
 5. Member has significant symptomatic anemia (defined as hemoglobin (Hgb) less than 10 g/dL); **AND**
 6. Treatment with a first-line JAK inhibitor [e.g., ruxolitinib (Jakafi), fedratinib (Inrebic)] led to the development of anemia (defined as hemoglobin (Hgb) less than 10 g/dL); **OR**
 - i. Treatment with a different JAK inhibitor [e.g., ruxolitinib (Jakafi), fedratinib (Inrebic)] has been deemed inappropriate due to pre-existing anemia (Hgb < 10 g/dL) prior to the initiation of therapy

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- II. Momelotinib (Ojjaara) is considered investigational when used for all other conditions, including but not limited to:
- A. Low-risk myelofibrosis
 - B. Polycythemia vera
 - C. Essential thrombocythemia
 - D. Anemia correction in the setting of chronic kidney disease (CKD)
 - E. Anemia correction in the setting of MDS or any other hematological condition
 - F. Graft versus host disease
 - G. Lymphoproliferative neoplasms
 - H. Solid tumors (e.g., prostate, colorectal, lung)
 - I. 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. Medication will not be used in combination with another JAK inhibitor [e.g., ruxolitinib (Jakafi), fedratinib (Inrebic), pacritinib (Vonjo)]; **AND**
- IV. Member has exhibited improvement or stability of disease symptoms [e.g., transfusion independence, improvement in total symptom score (TSS), correction of splenomegaly]

Supporting Evidence

- I. Momelotinib (Ojjaara) is a Janus Kinase (JAK1, JAK2) and Activin Type I receptor (ACVR1) inhibitor, expected to be FDA-approved for adult patients with myelofibrosis (MF), who were previously treated with a JAK inhibitor and had hematologic suppression (anemia). It is orally administered at 200 mg once daily. Efficacy and safety of momelotinib (Ojjaara) has not been studied in pediatric population.
- II. Myelofibrosis (MF) is a cancer of the bone marrow. It is a rare myeloproliferative neoplasm (MPN) where scar-like tissue replaces functional bone marrow, leading to abnormal blood cells. MF may progress to acute myeloid leukemia. The incidence of MF is 1/100,000 people per year, with roughly 21,000 cases in the US. An estimated 54% of these are anemic [hemoglobin (Hgb) <10 g/dL] requiring blood transfusions. At onset and throughout disease progression, MF may present high symptom burden with non-specific constitutional symptoms (e.g., fatigue, shortness of breath, bleeding, bone pain, abdominal pain) and splenomegaly. Over time MF may progress to acute myeloid leukemia (AML) and current incidence of such leukemic transformation is one in five patients (up to 20%).
- III. There are five risk levels of disease that correlate with prognosis of MF, and treatment is based on risk stratification. When patients are not eligible for allogeneic stem cell transplant, symptom targeted therapy may be used in those with intermediate or higher risk MF. Treatment goals include reduction of spleen size and symptom burden. Symptomatic therapies include hydroxyurea and JAK inhibitors: ruxolitinib (Jakafi), fedratinib (Inrebic), pacritinib (Vonjo).

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- IV. JAK inhibitors have only been sufficiently evaluated in patients with at least intermediate-risk MF and have unknown clinical value for lower risk disease. JAK inhibitors do not reverse fibrosis or prolong survival but may reduce spleen size and improve disease-related symptoms. In absence of splenomegaly and symptoms, these medications have unknown application. Given the specialized diagnosis, treatment, and monitoring, prescribing by or in consultation with a specialist is required.
- V. Notably, JAK inhibitor therapy may exacerbate anemia and thrombocytopenia. Pacritinib (Vonjo) is recommended as NCCN Category 1 recommended agent for patients with severe thrombocytopenia (platelets $< 50 \times 10^9/L$), while for those with anemia (Hgb < 10 g/dL), erythropoietin alfa (Epogen), danazol, and lenalidomide (Revlimid) are guideline-directed therapies along with RBC transfusions. Notably, patients with erythropoietin (EPO) levels < 500 mU/mL may be good candidates for erythropoiesis stimulating agents (ESA, e.g., Retacrit, Procrit), while those with EPO > 500 mU/mL require therapy with danazol or lenalidomide.
- VI. Mometotinib (Ojjaara) is the fourth JAK inhibitor in the MF therapy landscape, but the first agent with ACVR1 activity. It is expected to be specifically approved in those with severe anemia due to first-line therapies [e.g., HU, Jakafi, Inrebic], and may serve as an alternative to danazol and lenalidomide (Revlimid). It may also be considered a first-line agent for treatment-naïve MF patients with severe anemia at the onset. NCCN guidelines have not been updated to include momelotinib (Ojjaara).
- VII. Mometotinib (Ojjaara) was studied in phase 3, randomized (2:1), double-blind, double-dummy clinical trial (MOMENTUM; N= 195) to assess the superiority of momelotinib (Ojjaara) versus danazol in symptomatic, anemic patients with a history of JAK inhibitor therapy. Patients: transplant-ineligible adults with intermediate or high-risk MF, palpable splenomegaly, JAK inhibitor therapy (≥ 90 days) complicated by anemia (Hgb ≤ 10 g/dL) and RBC transfusion ≥ 4 units in eight weeks; and mean (SD) Myelofibrosis Symptom Assessment Form- Total Symptom Score (MFSAF-TSS) of 25 (12.8).
- VIII. The MOMENTUM clinical trial reported superiority of momelotinib (Ojjaara) to danazol with respect to TSS response rate showing a statistically significant treatment difference of 16% in favor of momelotinib (Ojjaara) (p 0.00095). Additionally, higher percentage of patients in momelotinib arm reported transfusion independence rates (13.58%, p0.0064, non-inferior to danazol). Additional secondary endpoints, namely, $>25\%$ splenic response rate (34% treatment difference, p <0.0001), mean (SD) absolute TSS change from baseline to week 24 (-6.5, p 0.0014), and rate of zero transfusion at week 24 (18% treatment difference, p 0.0012) were in favor of momelotinib (Ojjaara) versus danazol establishing statistically significant superiority in the clinical trial setting.
- IX. Exploratory secondary endpoints of the MOMENTUM trial, overall survival, and leukemia-free survival were not statistically significant but showed numeric favorability to momelotinib (Ojjaara) with hazard ratios (HR) of 0.73 and 0.65, respectively. Additional phase 3 non-inferiority trials of momelotinib (Ojjaara): versus ruxolitinib (Jakafi) in JAK inhibitor-naïve anemic patients (SIMPLIFY-1; N= 432); and versus best available therapy in JAK-inhibitor experienced patients (SIMPLIFY-2; N= 156) failed to achieve non-inferiority of momelotinib (Ojjaara) with the comparator. However, participants in both trials achieved favorable transfusion independence for ≥ 12 weeks.
- X. It should be noted that momelotinib (Ojjaara), when compared with ruxolitinib (Jakafi) in JAK inhibitor naïve population with MF (SIMPLIFY-1 clinical trial) did not exhibit statistically significant non-inferiority assessed via TSS response rate. At this time, magnitude of efficacy of

momelotinib (Ojjaara) as a first-line therapy for MF in JAK-inhibitor naïve population, is unknown.

- XI. MOMENTUM clinical program demonstrated the superiority of momelotinib (Ojjaara) versus danazol in JAK inhibitor refractory population across multiple key endpoints demonstrating disease morbidity advantage. TSS response rate is a validated measure of treatment response and reflects constitutional improvement in quality of life. Momelotinib (Ojjaara) therapy led to a higher transfusion independence rate and reduction in splenomegaly, which supports the clinical value of momelotinib (Ojjaara). At this time, the long-term efficacy of momelotinib (Ojjaara) in reducing leukemic transformation, improving overall survival, as well as achieving long-term disease stability – remains undetermined.
- XII. During the MOMENTUM trial, the safety profile for momelotinib (Ojjaara) was comparable to that of danazol. Overall, severe (grade ≥ 3), adverse events (AEs) between arms were 53.8% and 64.6%, respectively. The most common hematological AE included anemia (99% vs 100%), thrombocytopenia (76% vs 61%), and neutropenia (29% vs 26%). Common AE for momelotinib versus danazol respectively, included diarrhea (22% vs 9%), nausea (16% vs 9%), asthenia (13% vs 9%), pruritis (11% for both arms), and acute kidney injury (4.6% vs 12%).
- XIII. During the treatment phase, 23 (18%) patients in the momelotinib (Ojjaara) arm and 15 (23%) in the danazol arm discontinued therapy due to AE. The long-term safety of momelotinib (Ojjaara) remains undetermined.
- XIV. Current clinical evidence for momelotinib (Ojjaara) provides indicators of efficacy and supports its place in therapy as an applicable therapeutic alternative in transplant-ineligible anemic patients with palpable splenomegaly when front-line JAK inhibitor therapy is complicated by anemia. The majority of patients, who are intolerant to first-line JAK inhibitors (e.g., ruxolitinib, fedratinib) due to the development of symptomatic anemia, may be candidates for second-line therapy with momelotinib (Ojjaara). Additionally, patients, who have pre-existing symptomatic anemia (Hgb < 10 g/dL) and for whom first-line JAK inhibitor therapy would be deemed inappropriate, may benefit from the anemia correction potential of this drug.

Investigational or Not Medically Necessary Uses

- I. Momelotinib (Ojjaara) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Low-risk myelofibrosis
 - B. Polycythemia vera
 - C. Essential thrombocythemia
 - D. Anemia correction in the setting of chronic kidney disease (CKD)
 - E. Anemia correction in the setting of MDS or any other hematological condition
 - F. Graft versus host disease
 - G. Lymphoproliferative neoplasms
 - H. Solid tumors (e.g., prostate, colorectal, lung)
 - I. 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*

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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.

References

1. Ojjaara [Prescribing Information]. GlaxoSmithKline, Durham, NC. September 2023.
2. Verstovsek S, Gerds AT, et al. Lancet. 2023 Jan 28;401(10373):269-280. Erratum in: Lancet. 2023 Apr 29;401(10386):1426.
3. Mesa RA, Kiladjian JJ, et al. J Clin Oncol. 2017 Dec 1;35(34):3844-3850.
4. Harrison CN, Vannucchi AM, et al. Lancet Haematol. 2018 Feb;5(2):e73-e81.

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
fedratinib (Inrebic) Policy	Myelofibrosis
ruxolitinib (Jakafi, Opzelura)	Myelofibrosis, polycythemia vera, GVHD
pacritinib (Vonjo)	Myelofibrosis with severe thrombocytopenia (platelet count below 50 x 10 ⁹ /L)

Policy Implementation/Update:

Action and Summary of Changes	Date
Removed split fill from policy	05/2025
Policy created	09/2023

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP047

Description

Medications included in this policy are subcutaneous and oral disease modifying therapies for the treatment of multiple sclerosis.

Length of Authorization

Cladribine (Mavenclad) only

- Initial: 12 months
- Renewal: Two months, maximum of one renewal per lifetime

All other agents

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
cladribine (Mavenclad)	Relapsing forms of multiple sclerosis (MS)	10 mg tablets (box of 4 tablets)	1 box (4 tablets)/26 days*
		10 mg tablets (box of 5 tablets)	1 box (5 tablets)/26 days*
		10 mg tablets (box of 6 tablets)	1 box (6 tablets)/26 days*
		10 mg tablets (box of 7 tablets)	1 box (7 tablets)/26 days*
		10 mg tablets (box of 8 tablets)	1 box (8 tablets)/26 days*
		10 mg tablets (box of 9 tablets)	1 box (9 tablets)/26 days*
		10 mg tablets (box of 10 tablets)	1 box (10 tablets)/26 days*
daclizumab (Zinbryta)		150mg/mL single-dose PFS [±]	1 syringe/28 days
dimethyl fumarate (Tecfidera, dimethyl fumarate)		30 day starter pack	1 starter pack/30 days (60 capsules/30 days)
		120 mg capsule	60 capsules/30 days
	240 mg capsule	60 capsules/30 days	
monomethyl fumarate (Bafiertam)	95 mg capsule	120 capsules/30 days	
diroximel fumarate (Vumerity)		231 mg capsule	120 capsules/30 days

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fingolimod (Gilenya, fingolimod)	Relapsing forms of multiple sclerosis (MS)	0.25 mg capsule	30 capsules/30 days
		0.5 mg capsule	30 capsules/30 days
fingolimod lauryl sulfate (Tascenso ODT)		0.25 mg tablet disintegrating	30 tablets/30 days
		5 mg tablet disintegrating	30 tablets/30 days
glatiramer acetate (Copaxone, Glatopa, glatiramer acetate)		20 mg/mL single dose PFS	30 syringes per/30 days
glatiramer acetate (Copaxone, Glatopa, glatiramer acetate)		40 mg/mL single dose PFS	12 syringes/28 days
interferon beta-1a (Avonex)		30 mcg/0.5mL PFS	4 syringes (1 kit)/28 days
		30 mcg/0.5mL pen	4 pens/28 days
interferon beta-1a (Plegridy)		Starter Pack – (Pen Injector or PFS)	1 starter pack/28 days
		125 mcg/0.5mL (Pen Injector or PFS)	2 pens (or PFS)/28 days
interferon beta-1a (Rebif)		22 mcg/0.5mL (Auto-injector or PFS)	12 syringes/28 days
		44 mcg/0.5mL (Auto-injector or PFS)	12 syringes/28 days
		Titration Pack (PFS or Solution)	1 pack (12 syringes)/28 days
interferon beta-1b (Betaseron)		0.3 mg powder for reconstitution	14 syringes/28 days
interferon beta-1b (Extavia)		0.3 mg powder for reconstitution	15 syringes/30 days
ofatumumab (Kesimpta)			20 mg/0.4mL Auto-injector
ozanimod (Zeposia)	Relapsing forms of multiple sclerosis (MS); Ulcerative colitis**	7-Day Starter Pack (0.23 mg, 0.46 mg)	7 capsules/7 days
		Starter Kit (7-day starter pack and 0.92 mg 30-count bottle)	37 capsules/37 days
		Starter Kit (7-day starter pack and 0.92 mg 21-count bottle)	28 capsules/28 days
		0.92 mg capsules	30 tablets/30 days
ponesimod (Ponvory)		2-10 mg starter pack	Initial: 14 tablets/14 days
		20 mg tablet	

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			Maintenance: 30 tablets/30 days
siponimod (Mayzent)	Relapsing forms of multiple sclerosis (MS)	0.25 mg starter pack (Titrate to 2 mg dose)	12 tablets/5 days
		0.25 mg tablets	28 tablets/28 days
		0.25 mg starter pack (Titrate to 1 mg dose)	7 tablets/4 days
		1 mg tablet	28 tablets/28 days
		2 mg tablets	30 tablets/30 days
teriflunomide (Aubagio, teriflunomide)		7 mg tablets	28 tablets/28 days
		14 mg tablets	28 tablets/28 days

*Maximum of 2 boxes/331 days

±PFS: Prefilled Syringe

**For ozanimod (Zeposia) in ulcerative colitis: Reference Chronic Inflammatory Disease policy

Initial Evaluation

generic dimethyl fumarate, generic fingolimod, glatiramer acetate (Glatopa), generic glatiramer acetate, and generic teriflunomide are the preferred generic agents.

- There is no prior authorization* required on these preferred agents, unless requesting over the allowed quantity limits noted above.

interferon beta-1a (Avonex; Rebif), diroximel fumarate (Vumerity), and ofatumumab (Kesimpta) are preferred agents.

- There is no prior authorization required on these preferred agents, unless requesting over the allowed quantity limits noted above. Step therapy may apply.

*Brand Aubagio, Copaxone, Gilenya, and Tecfidera are noncovered drugs given generic availability, nonformulary multi-source brand requirements apply

- I. **Cladribine (Mavenclad), daclizumab (Zinbryta), fingolimod lauryl sulfate (Tascenso ODT), interferon beta-1a (Plegridy), interferon beta-1b (Betaseron), interferon beta-1b (Extavia), monomethyl fumarate (Bafiertam), ozanimod (Zeposia), and ponesimod (Ponvory) 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. Medication will be used as monotherapy for multiple sclerosis; **AND**
 - C. Multiple sclerosis (MS) diagnosis is confirmed and documented by laboratory report (e.g. MRI); **AND**
 - D. A diagnosis of one of the following:
 1. **Relapsing-Remitting MS (RRMS) or Clinically Isolated Syndrome (CIS); OR**
 2. **Active Secondary Progressive MS (SPMS); AND**
 - i. Active disease confirmed by clinical relapses or MRI evidence of contrast enhancing lesions and/or new or unequivocally enlarging T2 lesions; **AND**
 - E. Documentation of treatment with at least three of the following have been ineffective or not tolerated, or ALL are contraindicated: interferon beta-1a (Avonex; Rebif), generic dimethyl fumarate, generic fingolimod, glatiramer acetate/Glatopa, generic teriflunomide, diroximel fumarate (Vumerity), or ofatumumab (Kesimpta).

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- II. **Brand Aubagio, Brand Gilenya, Brand Tecfidera and Brand Copaxone** may be considered medically necessary when the following criteria below are met:
- A. Criteria I(A)-I(D) 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**
 - 1. The prescriber must document one or more of the following, indicating that the reaction:
 - i. Was life-threatening; **OR**
 - ii. Required hospitalization; **OR**
 - iii. Required intervention to prevent impairment or damage; **OR**
 - 2. 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**
 - 3. 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 perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
 - i. More than one generic equivalent has been tried, or there is only one generic equivalent for the prescribed brand drug; **AND**
 - D. **For Brand Aubagio:** Documentation of treatment with all six (1, 2, 3, 4, 5, and 6) of the following have been ineffective, contraindicated, or not tolerated:
 - 1. interferon beta-1a (Avonex; Rebif)
 - 2. glatiramer acetate (Glatopa) or generic glatiramer acetate
 - 3. generic dimethyl fumarate
 - 4. generic fingolimod
 - 5. diroximel fumarate (Vumerity);
 - 6. ofatumumab (Kesimpta); **OR**
 - E. **For Brand Gilenya:** Documentation of treatment with all six (1, 2, 3, 4, 5, and 6) of the following have been ineffective, contraindicated, or not tolerated:
 - 1. interferon beta-1a (Avonex; Rebif)
 - 2. glatiramer acetate (Glatopa) or generic glatiramer acetate
 - 3. generic dimethyl fumarate
 - 4. generic teriflunomide
 - 5. diroximel fumarate (Vumerity);
 - 6. ofatumumab (Kesimpta); **OR**
 - F. **For Brand Tecfidera:** Documentation of treatment with all six (1, 2, 3, 4, 5, and 6) of the following have been ineffective, contraindicated, or not tolerated:
 - 1. interferon beta-1a (Avonex; Rebif)
 - 2. generic fingolimod

3. glatiramer acetate (Glatopa) or generic glatiramer acetate
 4. generic teriflunomide
 5. diroximel fumarate (Vumerity);
 6. ofatumumab (Kesimpta); **OR**
- G. **For Brand Copaxone:** Documentation of treatment with all six (1, 2, 3, 4, 5, and 6) of the following have been ineffective, contraindicated, or not tolerated:
1. interferon beta-1a (Avonex; Rebif)
 2. generic fingolimod
 3. generic dimethyl fumarate
 4. generic teriflunomide
 5. diroximel fumarate (Vumerity)
 6. ofatumumab (Kesimpta);
- III. **Siponimod (Mayzent)** may be considered medically necessary when the following criteria below are met:
- A. Criteria I(A)-I(E) above are met; **AND**
 - B. CYP2C9 genotype has been confirmed; **AND**
 - C. Member does not have a CYP2C9*3/*3 genotype
- IV. Medications listed above are considered investigational when used for all other conditions, including but not limited to:
- A. Primary Progressive MS (PPMS)

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. Prescriber attestation that the patient has demonstrated a clinical benefit with therapy, as defined by no relapses, less than two unequivocally new MRI-detected lesions, or lack of increased disability on examination over a one-year period; **AND**
- IV. If the request is **for Brand Aubagio, Brand Gilenya, Brand Tecfidera, or Copaxone:**
 - A. 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**
 - B. 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**
 - a. The prescriber must document one or more of the following, indicating that the reaction:
 - i. Was life-threatening; **OR**
 - ii. Required hospitalization; **OR**
 - iii. Required intervention to prevent impairment or damage; **OR**

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- b. 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**
 - c. 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 perform activities of daily living OR documentation of disease progression indicative of ineffectiveness; **AND**
 - i. More than one generic equivalent has been tried, or there is only one generic equivalent for the prescribed brand drug; **OR**
- V. If the request is for **siponimod (Mayzent)** and treatment has been interrupted for four or more consecutive daily doses, a re-titration starter package is covered by the manufacturer

Supporting Evidence

- I. **Siponimod (Mayzent):** Per the package label, if treatment with siponimod (Mayzent) is interrupted for FOUR or more consecutive daily doses after completion of initial titration, treatment should be reinitiated with Day 1 of the titration regimen, including first-dose monitoring when appropriate. Siponimod (Mayzent) manufacturer, Novartis, confirmed 5-day titration packs/starter pack will be shipped from HomeScripts mail order pharmacy at no charge to commercial plans. Even in cases where the member needs to re-titrate the starter pack is covered by Novartis via HomeScripts.
- II. American Academy of Neurology (AAN) guidelines recommend clinicians should offer DMTs to people with relapsing forms of MS with recent clinical relapses or MRI activity, guidelines do not contain treatment sequencing recommendations.
- III. AAN guidelines recommend clinicians should discuss switching from one DMT to another in people with MS who have been using a DMT long enough for the treatment to take full effect and are adherent to their therapy when they experience one or more relapses, two or more unequivocally new MRI-detected lesions, or increased disability on examination over a one-year period of using a DMT.
- IV. DMTs take a variable amount of time to become clinically active, and new lesion formation may occur after initiation but before the time of full efficacy, confounding interpretation of follow-up MRI scans. Consequently, many clinicians obtain new baseline MRI three to six months after initiating DMTs to monitor from a treated baseline. The optimal interval for ongoing monitoring is uncertain, as short-term stability as evidenced by clinical and MRI criteria may not consistently predict long-term stability.
- V. Per Lublin, et al. 2014, disease activity is determined by clinical relapses assessed at least annually and/or MRI activity (contrast-enhancing lesions; new or unequivocally enlarging T2 lesions).
- VI. The FDA Summary Review for Regulatory Action on the NDA for siponimod (Mayzent) states the following: In the active secondary progressive phase of the disease, patients can accrue disability both from acute relapses and from the progressive component of the disease. Active secondary progressive disease and relapsing-remitting disease overlap in evolution. Categorization as secondary progressive disease is based on clinical judgment; there are no clinical findings or biomarkers that meaningfully define or predict the phenotypes of relapsing

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forms of MS. A continued progression of disability with no concurrent inflammatory activity and no clinical relapses is described as a non-active secondary progressive MS. Importantly, to support an indication for the treatment of secondary progressive MS (as distinct from active secondary progressive MS), it is critical that efficacy be established in patients who have non-active secondary progressive MS (SPMS), and that the drug effect be clearly distinguished from an effect on inflammatory demyelination and clinical relapses that are present in patients with active SPMS (a relapsing form of MS). Multiple drugs have been approved for the treatment of relapsing forms of MS. Conversely, there is a significant unmet medical need for the treatment of non-active SPMS..... The indication supported by the submitted data is therefore for the treatment of relapsing forms of MS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. It must be emphasized that thirteen different therapies have been approved to treat relapsing forms of multiple sclerosis, and that the population for which siponimod will be indicated is the same as for those drugs. The siponimod labeling will be the first explicitly describing that relapsing forms of multiple sclerosis include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, but all sponsors of the drugs approved for the treatment of relapsing forms of multiple sclerosis will be requested to update their indication statements to conform with this contemporary nomenclature.

- VII. 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:
 - Contain the same active/key ingredient
 - Have the same strength
 - Use the same dosage form (for instance, a table, capsule, or liquid) and
 - Use the same route of administration (for instance, oral, topical, or injectable)
- VIII. 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.
 - Thus, when an adverse reaction or allergy occurs to any medication (brand or generic), it is important to report to MedWatch.
 - 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.
- IX. 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.
 - 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

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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.

X. Tools used in diagnosis of MS:

MS with a relapsing-remitting course	
Based upon two separate areas of damage (dissemination in space) in the CNS that have occurred at different points in time (dissemination in time). Unless contraindicated, MRI should be obtained.	
Dissemination in <u>time</u> (Development/appearance of new CNS lesions over time)	Dissemination in <u>space</u> (Development of lesions in distinct anatomical locations within the CNS)
≥ 2 clinical attacks; OR 1 clinical attack AND one of the following: - MRI indicating simultaneous presence of gadolinium-enhancing and non-enhancing lesions at any time or by a new T2-hyperintense or gadolinium-enhancing lesion on follow-up MRI compared to baseline scan - CSF-specific oligoclonal bands	≥ 2 lesions; OR 1 lesion AND one of the following: - Clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location - MRI indicating ≥ 1 T2-hyperintense lesions characteristic of MS in ≥ 2 of 4 areas of the CNS (periventricular, cortical or juxtacortical, infratentorial, or spinal cord)
Secondary progressive MS course	
- MS course characterized by steadily increasing objectively documented neurological disability independent of relapses. Fluctuations, periods of stability, and superimposed relapses might occur. Secondary progressive multiple sclerosis, is further distinguished as a progressive course following an initial relapsing-remitting course. - Diagnosed retrospectively based on previous year's history.	

Investigational Uses or Not Medically Necessary Uses

I. Primary Progressive MS

- A. All agents included in this policy have not been evaluated in or have not been found to have a positive effect on progression in the setting of PPMS.

References

1. daclizumab (Zinbryta)[Prescribing Information]. Biogen Inc. Cambridge, MA. May 2016
2. teriflunomide(Aubagio)[Prescribing Information]. Sanofi. Cambridge, MA. January 2016
3. Interferon beta-1a (Avonex) [Prescribing Information]. Biogen Idec Inc. Cambridge, MA. May 2006
4. Interferon beta-1a (Rebif) [Prescribing Information]. Serono, Inc. September 2005
5. Peginterferon beta-1a (Plegridy) [Prescribing Information]. Biogen Idec Inc. Cambridge, MA. Revised July 2016
6. Interferon beta-1b (Betaseron) [Prescribing Information]. Berlex Laboratories. Revised October 2006
7. Interferon beta-1b (Extavia) [Prescribing Information]. Bayer Health Care Pharmaceuticals Inc. Whippany, NJ. Revised November 2017
8. glatiramer acetate (Copaxone) [Prescribing Information]. Teva Pharmaceuticals, Inc., Revised February 2004

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9. glatiramer acetate (Glatopa) [Prescribing Information]. Sandoz Inc., Princeton, NJ. Revised June 2015
10. Generic glatiramer acetate [Prescribing Information]. Mylan Pharmaceuticals Inc. Morgantown, WV. April 2017
11. fingolimod (Gilenya) [Prescribing Information]. East Hanover, NJ: Novartis Corp. Revised August 2015
12. dimethyl fumarate (Tecfidera) [Prescribing Information]. Biogen Idec Inc. Cambridge, MA. January 2013
13. Mayzent [Prescribing Information]. Novartis Pharmaceuticals Corporation: East Hanover, NJ. March 2019.
14. ozanimod (Zeposia) [Prescribing Information]. Celgene Corporation. Summit, NJ. March 2020.
15. Kappos L, Bar-Or A, Cree BAC, et al. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. *The Lancet*. 2018;391(10127):1263-1273.
16. Siponimod for the Treatment of Secondary Progressive Multiple Sclerosis: Effectiveness and Value: Draft Evidence Report. Institute for Clinical and Economic Review. 2019. Available at: https://icer-review.org/wp-content/uploads/2018/10/ICER_MS_Draft_Evidence_Report_031419.pdf
17. American Academy of Neurology. Practice Guideline: Disease-modifying Therapies for Adults with Multiple Sclerosis. 2018; <https://www.aan.com/Guidelines/home/GetGuidelineContent/900>. Accessed April 18, 2019.
18. UpToDate, Inc. Clinical presentation, course, and prognosis of multiple sclerosis in adults. UpToDate [database online]. Waltham, MA. Last updated Sept 28, 2018 Available at: <http://www.uptodate.com/home/index.html>.
19. UpToDate, Inc. Treatment of progressive multiple sclerosis in adults. UpToDate [database online]. Waltham, MA. Last updated Nov 28, 2018 Available at: <http://www.uptodate.com/home/index.html>.
20. UpToDate, Inc. Evaluation and diagnosis of multiple sclerosis in adults. UpToDate [database online]. Waltham, MA. Last updated Apr 05, 2019 Available at: <http://www.uptodate.com/home/index.html>.
21. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 2018;17(2):162-173.
22. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014;83(3):278-86.
23. Center for Drug Evaluation and Research. Application Number 209884Orig1s000 Summary Review. Summary Review for Regulatory Action: NDA209884. Updated March 26, 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/209884Orig1s000SumR.pdf
24. Hauser SL, Bar-or A, Cohen JA, et al. Ofatumumab versus Teriflunomide in Multiple Sclerosis. *N Engl J Med*. 2020;383(6):546-557.
25. ofatumumab (Kesimpta) [Prescribing Information]. East Hanover, NJ; Novartis. August 2020.
26. Kappos L, Burcklen M, Freedman MS, et al. Efficacy and safety of ponesimod compared to teriflunomide in patients with relapsing multiple sclerosis: results of the randomized, active-controlled, double-blind, parallel-group phase 3 OPTIMUM study [oral presentation]. Presented at: The 35th European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) Congress; September 11-13, 2019; Stockholm, SE.
27. monomethyl fumarate (Bafiertam) [Prescribing Information]. High Point, NC; Banner Life Sciences LLC. April 2020.

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated criteria to allow for brand use when there is an intolerance	03/2025
Live 12/1/2024: Removed PA and added Kesimpta and Rebif to preferred agents with single step. Updated step requirement for non-preferred brands from trial of 2 to requiring trial of 3 preferred agents. Addition of Rebif and Kesimpta to MSB step/criteria. Removed criteria for Extavia that required trial of Betaseron, aligned with non-preferred brand products.	11/2024
Live 07/01/2023: Updated box around preferred agents not requiring prior authorization. Added new Zeposia formulations to QL table.	06/2023
Included new generic teriflunomide. Branded product updated to align with requirements for other multi-source brands (i.e., Gilenya Copaxone, Tecfidera).	03/2023
Added Tascenso ODT 5mg disintegrating tablet to QL table	01/2023
Effective 01/01/2023 - Updated diroximel fumarate (Vumerity) as a preferred product	12/2022
Included newly available generic fingolimod as preferred product, replacing brand formulation. Branded product updated to align with requirements for other multi-source brands (i.e., Copaxone, Tecfidera).	11/2022
Added Tascenso ODT to policy	09/2022
Added 0.25 (1mg) starter pack and 1 mg dose of Mayzent to policy	04/2022

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Added renewal of brand Copaxone into policy aligning with requirements for brand Tecfidera requiring medical necessity for brand over generic; Updated teriflunomide (Aubagio) as a preferred product effective 1/1/2022.	11/2021
Update to initial requests for brand Tecfidera or brand Copaxone to require trial of Avonex, Gilenya, and glatiramer acetate (Glatopa)/generic glatiramer acetate for brand Tecfidera requests; and trial of Avonex, Gilenya, and generic dimethyl fumarate for brand Copaxone requests	05/2021
Adding loading dose to QL table for Kesimpta	02/2021
Addition of brand Copaxone into policy aligning with requirements for brand Tecfidera requiring medical necessity for brand over generic.	12/2020
Addition of ofatumumab (Kesimpta) and ponesimod to policy within non-preferred position. Addition of brand Tecfidera criteria requiring medical necessity for brand over generic.	11/2020
Updated preferred products to specify generic dimethyl fumarate upon new generic availability (effective 10/2020). Removed criteria specific to branded Copaxone. Addition of monomethyl fumarate (Bafiertam) to policy within non-preferred position.	09/2020
Updated to include ozanimod (Zeposia) as a non-preferred product	04/2020
Updated fingolimod (Gilenya) as a preferred product effective 4/1/2020 per WA PDL update	03/2020
Updated to add non-preferred Vumerity	11/2019
Updated to include box around preferred agents not requiring prior authorization	10/2019
Updated to new policy format. Added newly approved drugs Mayzent and Mavencald. Added question requiring diagnosis confirmed and documented by laboratory report (e.g., MRI).	08/2019
Policy created from criteria	11/2017

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP166

Split Fill Management*

Description

Lenvatinib (Lenvima), pazopanib (Votrient), and sorafenib (Nexavar) are orally administered multi-tyrosine kinase inhibitors (multi-TKIs), which limit angiogenesis via the inhibition of the bindings of multiple tyrosine kinase enzymes to cell surface receptors (e.g., VEGF, FGFR, IL-2 receptor)

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
lenvatinib (Lenvima)	Unresectable Hepatocellular Carcinoma; Advanced Renal Cell Carcinoma; Recurrent, High-risk or Metastatic Endometrial Carcinoma; Locally Recurrent or Metastatic Progressive Thyroid Cancer	4 mg capsule therapy pack	30 capsules/30 days*
		10 mg capsule therapy pack	30 capsules/30 days*
		14 mg capsule therapy pack	60 capsules/30 days*
	Unresectable Hepatocellular Carcinoma	8 mg capsule therapy pack	60 capsules/30 days*
		12 mg capsule therapy pack	90 capsules/30 days*
	Advanced Renal Cell Carcinoma; Recurrent, High-risk or Metastatic Endometrial Carcinoma	18 mg capsule therapy pack	90 capsules/30 days*
		20 mg capsule therapy pack	60 capsules/30 days*
	Locally Recurrent or Metastatic Progressive Thyroid Cancer	24 mg capsule therapy pack	90 capsules/30 days*
pazopanib (Votrient)	Advanced Renal Cell Carcinoma; Advanced Soft Tissue Sarcoma	200 mg tablets	120 tablets/30 days
generic pazopanib			
sorafenib (Nexavar)	Desmoid Tumors	200 mg tablets	60 tablets/30 days
	Unresectable Liver Carcinoma; Advanced Renal Cell Carcinoma; Locally Recurrent or Metastatic Progressive Thyroid Cancer	200 mg tablets	120 tablets/30 days
generic sorafenib tosylate			
	Desmoid Tumors	200 mg tablets	60 tablets/30 days

*Quantity limits are based on recommended daily dose of lenvatinib (Lenvima) for each indication; QL exceptions allowed only for dose reductions

Initial Evaluation

- I. **Lenvatinib (Lenvima), pazopanib (Votrient), generic pazopanib, sorafenib (Nexavar), or generic sorafenib tosylate** may be considered medically necessary when the following criteria 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. The member has not experienced disease progression while on other multi-TKIs [e.g., lenvatinib (Lenvima), pazopanib (Votrient), sorafenib (Nexavar)] unless outlined below (e.g., Renal Cell Carcinoma); **AND**
 - D. A diagnosis of one of the following:
 1. **Renal Cell Carcinoma (RCC); AND**
 - i. The member has advanced (relapsed, stage III) or metastatic (stage IV) disease; **AND**
 - ii. The request is for first-line systemic therapy; **AND**
 - a. Lenvatinib (Lenvima) is being requested in combination with pembrolizumab (Keytruda); **OR**
 - iii. The request is for subsequent-line systemic therapy; **AND**
 - a. The member has had disease progression on, or intolerance to, **one** anti-angiogenic therapy unless all are contraindicated (e.g., axitinib [Inlyta], bevacizumab [Avastin], cabozantinib [Cabometyx]); **AND**
 - i. The request is for Lenvatinib (Lenvima) in combination with everolimus (Afinitor); **OR**
 - ii. The request is for monotherapy with pazopanib (Votrient); **AND**
 1. Request is for generic pazopanib; **OR**
 - a. Treatment with generic pazopanib is contraindicated or was not tolerated; **OR**
 - iii. The request is for monotherapy with generic sorafenib tosylate; **OR**
 1. Request for brand sorafenib tosylate (Nexavar) and documentation of intolerance or contraindication to generic sorafenib tosylate; **OR**
 2. **Hepatocellular Carcinoma (HCC); AND**
 - i. The member has unresectable, advanced (stage III) or metastatic (stage IV) disease; **AND**
 - ii. The medication will be used as monotherapy; **AND**
 - iii. The request is for generic sorafenib tosylate; **AND**
 - a. Provider attests the member is Child-Pugh Class A or Class B7; **OR**
 - iv. Request for brand sorafenib tosylate (Nexavar) and documentation of intolerance or contraindication to generic sorafenib tosylate; **AND**
 - a. Provider attests the member is Child-Pugh Class A or Class B7; **OR**
 - v. The request is for lenvatinib (Lenvima); **AND**
 - a. Provider attests the member has Child-Pugh Class A; **OR**
 3. **Thyroid Carcinoma; AND**
 - i. The member has locally recurrent or metastatic (stage IV) disease; **AND**
 - ii. The member has one of the following subtypes of differentiated thyroid carcinoma:

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- a. Papillary thyroid carcinoma; **OR**
 - b. Follicular thyroid carcinoma; **OR**
 - c. Hurthle cell thyroid carcinoma; **AND**
 - iii. The disease is refractory to radioactive iodine treatment (RAI); **AND**
 - iv. The request is for monotherapy with lenvatinib (Lenvima); **OR**
 - v. The request is for monotherapy with generic sorafenib tosylate; **OR**
 - a. Request for brand sorafenib tosylate (Nexavar) and documentation of intolerance or contraindication to generic sorafenib tosylate; **OR**
- 4. Soft Tissue Sarcoma (STS); AND**
- i. The member has advanced (unresectable) or metastatic (stage IV) soft tissue sarcoma (STS); **AND**
 - ii. The diagnosis of soft tissue sarcoma (STS) does not include the following histological subtypes:
 - a. Gastrointestinal Stromal Tumors (GIST); **OR**
 - b. Adipocytic Sarcoma (Liposarcoma); **AND**
 - iii. The request is for pazopanib (Votrient); **AND**
 - a. The medication will be used as monotherapy; **AND**
 - b. The member has had disease progression on at least one anthracycline-based chemotherapy regimen unless all are contraindicated (e.g., doxorubicin, epirubicin, ifosfamide); **AND**
 - i. Request is for generic pazopanib; **OR**
 - 1. Treatment with generic pazopanib has been ineffective, contraindicated, or not tolerated; **OR**
- 5. Endometrial Carcinoma (EC); AND**
- i. The member has advanced, or metastatic endometrial carcinoma (EC); **AND**
 - ii. The disease is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR); **AND**
 - iii. The member had disease progression on, or after, at least ONE platinum-based systemic chemotherapy in the first-line setting; **AND**
 - iv. The request is for lenvatinib (Lenvima); **AND**
 - a. Lenvatinib (Lenvima) will be used in combination with pembrolizumab (Keytruda); **OR**
- 6. Desmoid Tumors (DT); AND**
- i. The member has a diagnosis of desmoid tumors confirmed by:
 - a. An image-guided (CT or ultrasound) core needle or surgical biopsy of the tumor site; **AND**
 - b. Confirmation of diagnosis by a soft tissue pathologist; **AND**
 - c. Provider attestation that other germline mutation syndromes (i.e., familial adenomatous polyposis [FAP], Gardner syndrome) and/or myofibroblastic diseases (e.g., sarcoma, gastrointestinal stromal tumor, nodular fasciitis, leiomyoma) have been ruled out; **AND**
 - ii. The member has documentation of tumor progression within the last 6 months; **OR**
 - a. There is documentation of potential for morbidity (e.g., impairing, or threatening function, physical deformity); **OR**
 - b. There is documentation of significant symptoms (e.g., severe pain) **AND;**

- iii. The medication is not used in combination with any other oncology therapy; **AND**
 - iv. The request is for generic sorafenib tosylate; **OR**
 - a. Request for brand sorafenib tosylate (Nexavar) and there is documentation of intolerance or contraindication to generic sorafenib tosylate.
- II. Sorafenib (Nexavar) is considered not medically necessary when criteria above are not met and/or when used for:
 - A. Sorafenib (Nexavar) in combination with erlotinib for Hepatocellular Carcinoma
- III. Lenvatinib (Lenvima), pazopanib (Votrient), sorafenib (Nexavar) are considered investigational when used for all other conditions, including but not limited to:
 - A. Gastrointestinal Stromal Tumor
 - B. Adipocytic Sarcoma/Liposarcoma

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. Disease response to treatment defined by stabilization of disease or decrease in tumor size or spread; **AND**
- IV. For brand sorafenib tosylate (Nexavar): documentation of intolerance or contraindication to generic sorafenib tosylate; **OR**
- V. For brand pazopanib (Votrient): documentation of intolerance or contraindication to generic pazopanib

Supporting Evidence

- I. Multi-kinase inhibitors [lenvatinib (Lenvima), pazopanib (Votrient), sorafenib (Nexavar)] exert their actions by inhibiting activities of multiple tyrosine kinases by depriving access to the Cdc37-Hsp90 molecular chaperone unit. This inhibitory activity leads to limiting angiogenesis via various cell surface receptors (e.g., VEGF, FGFR, IL-2 receptor). Multi-kinase inhibitors (multi-TKI) listed under this policy have received FDA-approval for patients 18 years and older. Efficacy and safety of these agents have not been established in the pediatric population.
- II. Many treatment options exist for the conditions listed in this policy (e.g., renal cell carcinoma, hepatocellular carcinoma, thyroid carcinoma and soft tissue carcinoma). Initial and further line therapies in these settings are contingent upon patient specific characteristics. Given the complexities surrounding diagnosis and treatment choices, targeted drug therapies such as multi-kinase inhibitors must be prescribed by, or in consultation with, an oncologist.

III. Multi-kinase inhibitors are considered medically necessary when used as monotherapy. Efficacy and safety of these agents has not been studied in combination with other agents, with the following exceptions: lenvatinib in combination with everolimus for the treatment of renal cell carcinoma, and lenvatinib in combination with pembrolizumab for the treatment of endometrial carcinoma and first-line therapy of renal cell carcinoma.

IV. **Renal Cell Carcinoma (RCC):**

- Sorafenib (Nexavar) was studied in one randomized, double-blind, placebo-controlled, multicenter, Phase 3 trial and one randomized, Phase 2 discontinuation trial. The Phase 2 trial enrolled 202 patients with advanced RCC and included patients with no prior therapy and tumor histology other than clear cell carcinoma. Patients were on therapy for 12 weeks and then randomized to continue sorafenib (Nexavar) or switch to placebo. Sorafenib (Nexavar) had a progression free survival (PFS) of 163 days compared to 41 days for placebo ($p=0.0001$). The Phase 3 trial included 769 patients with advanced RCC who had received on prior systemic therapy. The primary endpoints included OS and PFS. The median PFS was 167 days for sorafenib (Nexavar) compared to 84 days for placebo with a HR of 0.44 (95% CI 0.35, 0.55).
- Recently, the NCCN guidelines have been updated to favor the use of multi-TKI in combination with immune checkpoint inhibitors (e.g., nivolumab, pembrolizumab). Lenvatinib (Lenvima) in combination with pembrolizumab (Keytruda) was recently studied in a phase 3, randomized, open-label trial (CLEAR study, N=1069) in comparison with lenvatinib (Lenvima) + everolimus (Afinitor), and sunitinib (1:1:1 randomization). PFS was longer with lenvatinib plus pembrolizumab than with sunitinib (median, 23.9 vs. 9.2 months; HR 0.39; 95% CI, 0.32 to 0.49; $P<0.001$) and was longer with lenvatinib plus everolimus than with sunitinib (median, 14.7 vs. 9.2 months; HR 0.65). Additionally, overall survival (OS) was longer with lenvatinib plus pembrolizumab than with sunitinib (HR 0.66; 95% CI, 0.49 to 0.88; $P = 0.005$). However, OS was not statistically different in lenvatinib plus everolimus when compared to sunitinib (HR 1.15; 95% CI, 0.88 to 1.50; $P = 0.30$).
- Additionally, lenvatinib (Lenvima) was studied in combination with everolimus (Afinitor) as a second-line regimen in one randomized, open-label, active-controlled, multicenter, Phase 1b/2 trial with 153 patients with advanced or metastatic RCC who had previously received anti-angiogenic therapy. The PFS for lenvatinib (Lenvima) in combination with everolimus (Afinitor) was 14.6 months compared to 5.5 months for everolimus (Afinitor) alone with a HR of 0.37 (95% CI 0.22, 0.62).
- Current NCCN guideline recommends pazopanib (Votrient) as 'other recommended regimen' in the first-line treatment setting, while sorafenib (Nexavar) has moved to 'useful in certain circumstances' as a subsequent-line option only with a category 3 recommendation. Circumstances for the use of sorafenib (Nexavar) are not defined in the NCCN guideline. Meta-analysis of clinical trials involving head-to-head comparison between multi-TKI shows that newer multi-TKI have better efficacy profile compared to sorafenib (Nexavar). Clinical trial for sorafenib (Nexavar) included patients with previous trials of interferon or cytokine-based regimens only, which are no longer used in the first-line setting.

V. **Hepatocellular Carcinoma (HCC):**

- Sorafenib (Nexavar) was studied in one randomized, double-blind, placebo-controlled, multicenter, Phase 3 trial in 602 patients with unresectable hepatocellular carcinoma (HCC). The primary endpoint was OS. Sorafenib (Nexavar) had an OS of 10.7 months compared to 7.9 months for placebo with a hazard ratio (HR) of 0.69 (95% CI 0.55, 0.87). The median time to progression was 5.5 months for sorafenib (Nexavar) and 2.8 months for placebo with a HR of 0.58 (95% CI 0.45, 0.74).
- Lenvatinib (Lenvima) was studied in one randomized, open-label, active-controlled, non-inferiority, Phase 3 trial in patients with previously untreated unresectable HCC (N=954). The primary efficacy endpoint was OS. Lenvatinib (Lenvima) had a median OS of 13.6 months compared to 12.3 months for sorafenib (Nexavar) with a HR of 0.92 (95% CI 0.79, 1.06). Lenvatinib (Lenvima) had a median PFS of 7.3 months compared to 3.6 months for sorafenib (Nexavar) with a HR of 0.64 (95% CI 0.55, 0.75).
- NCCN guideline for HCC was recently updated to include atezolizumab (Tecentriq) and bevacizumab (Avastin) as the preferred first-line therapy (category 1 recommendation). Sorafenib (Nexavar) and lenvatinib (Lenvima) are other recommended monotherapy options for first-line therapy (category 1) in patients with a Child-Pugh Class A score [or class A/ B7 for sorafenib (Nexavar)], and those who are treatment naïve in the first-line setting. Additionally, lenvatinib (Lenvima) and sorafenib (Nexavar) are also recommended as second-line agents with category 2A NCCN recommendations should there be progression on first-line therapy with atezolizumab (Tecentriq) and bevacizumab (Avastin). Additionally, it should be noted that incidence of hematological, respiratory, and hepatic adverse reactions is significant with a Tecentriq/Avastin regimen. In many situations, members discontinue the regimen due to adverse reactions and transition to multi-TKI agents without having progressed on the first-line therapy.
- NCCN guideline notes that sorafenib (Nexavar) may be used after disease progression on lenvatinib (Lenvima). However, there is no clinical data to support the use of lenvatinib (Lenvima) after disease progression with sorafenib (Nexavar). Neither of these therapies have been studied in large scale clinical trials to support the use after progression on the other. NCCN guidelines for HCC advise caution while using sorafenib (Nexavar) in patients with Child-Pugh Class B7. More than 95% of participants enrolled in the studies of sorafenib (Nexavar) as well as lenvatinib (Lenvima) had Child-Pugh score class A liver function. Safety data for patients with Child-Pugh score classes B or C are limited, and the recommended dose is uncertain. Additionally, in a systematic review meta-analysis of 8678 patients treated with first-line sorafenib therapy for advanced HCC, Child-Pugh B liver function was associated with a significantly worse OS compared with Child-Pugh A liver function (HR, 2.82 [95% CI, 2.04 to 3.92]; 4 studies). Estimated median OS was 7.2 months for the entire cohort, 8.8 months in patients with Child-Pugh A, and 4.6 months in patients with Child-Pugh B7.

VI. **Thyroid Carcinoma:**

- In the setting of thyroid carcinoma, sorafenib (Nexavar) was studied in one randomized, double-blind, placebo-controlled, multicenter, Phase 3 trial with 417 patients, who had locally recurrent or metastatic, progressively differentiated thyroid carcinoma. All participants were refractory to radioactive iodine (RAI) regimen. The primary efficacy

outcome was PFS. Sorafenib (Nexavar) had a median PFS of 10.8 months compared to 5.8 months for placebo with a HR of 0.59 (95% CI 0.46, 0.76).

- Lenvatinib (Lenvima) was studied in one randomized, double-blind, placebo-controlled Phase 3 trial in patients with locally recurrent or metastatic differentiated thyroid cancer refractory to RAI (N=392). The primary efficacy endpoint was PFS. Lenvatinib (Lenvima) had a median PFS of 18.3 months compared to 3.6 months for placebo with a HR of 0.21 (95% CI 0.16, 0.28).
- NCCN guidelines recommend lenvatinib (Lenvima) as the preferred regimen and sorafenib (Nexavar) as other recommended regimen for advanced and metastatic thyroid carcinoma (category 2A recommendations). NCCN considers lenvatinib (Lenvima) to be the preferred agent due to its response rate of 65% compared to 12% for sorafenib (Nexavar), although these agents have never been compared in head-to-head trials. Additionally, lenvatinib (Lenvima) and sorafenib (Nexavar) have not been studied in the settings of medullary and anaplastic thyroid carcinomas.

VII. **Soft Tissue Sarcoma (STS):**

- Pazopanib (Votrient) was studied as a targeted therapy option for the treatment of advanced Soft Tissue Sarcoma (STS) in one randomized, double-blind, placebo-controlled, multicenter, Phase 3 trial (N=369). Enrolled patients had metastatic STS who had failed at least one anthracycline-based chemotherapy regimen. Although patients with most histological subtypes of STS were included in this trial, patients with gastrointestinal stromal tumors (GIST) and adipocyte tumors (liposarcoma) were excluded (of note, there are around 50 histological subtypes of STS). Histological subtype patient distribution for this trial consisted of 47% leiomyosarcoma, 10% synovial sarcoma, and 47% other soft tissue sarcomas. The primary endpoint was PFS. Pazopanib (Votrient) significantly prolonged PFS at 4.6 months vs 1.6 months for placebo ($p < 0.0001$). There was no statistical difference between pazopanib (Votrient) and placebo for OS. NCCN guidelines recommend pazopanib (Votrient) as an option for palliative therapy for patients with progressive, unresectable, or metastatic STS with a category 2A recommendation.

VIII. **Endometrial Carcinoma (EC):**

- Advanced endometrial carcinomas have a poor prognosis, continued annual increase in incidence and disease related mortality. Nearly 84% of patients with recurrent endometrial carcinoma (EC) have microsatellite stable (MSS) or microsatellite-indeterminate tumors. Based on historical clinical trial data, although pembrolizumab is effective for microsatellite instability-high (MSI-H) disease (objective response rate (ORR), 57.1%), it appears less effective for MSS disease (best response was PR, 2/18 patients). Similarly, in a phase II study of lenvatinib monotherapy for advanced, previously treated, endometrial cancer, the ORR was 14.3% and the median PFS was 5.4 months. Thus, as monotherapy, lenvatinib and pembrolizumab do not have substantial evidence of efficacy for advanced EC. However, a novel approach to use these two agents in combination has been considered. Subsequent to FDA-approval, NCCN guideline for uterine carcinoma has provided a category 2A recommendation to the use of above combination, for the treatment of recurrent, high-risk and metastatic EC as a subsequent-line treatment option.
- Surgery is often the initial treatment for early-stage endometrial cancer and consists of a hysterectomy, often along with a salpingo-oophorectomy, and removal of lymph nodes.

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In some cases, depending on localized metastases, debulking may be required. Post-surgical adjuvant regimens may utilize radiation therapy and/ or platinum-based chemotherapy as preferred treatment options. For advanced stage (stage III or IV) EC, or when a member is not a candidate for surgery, systemic chemotherapy (platinum-based regimen preferred), and hormone therapy (e.g., tamoxifen, fulvestrant) are first-line treatment options.

- In a pivotal trial leading to US-FDA approval, Lenvatinib (Lenvima) was studied in combination with pembrolizumab (Keytruda) in a single-arm, open-label, Phase 1b/2 trial (Keynote146/ Study111; N=108) in patients with metastatic endometrial carcinoma after progression on at least one prior systemic therapy. All patients in this trial were exposed to platinum-based chemotherapy in the first-line setting. The primary efficacy outcome, ORR at week 24, was 38.3% (95% CI, 28.8, 47.8). Median duration of response (DoR) for responding participants was 21.2 months (95%CI; 7.6-NR). Additionally, a median PFS of 7.4 months (95% CI; 5.3-8.7) and a median OS of 16.7 months (95% CI; 15.0-NE) were reported. This led to an accelerated FDA approval of lenvatinib (Lenvima) for the treatment of EC in combination with pembrolizumab (Keytruda).
- As of August 2021, efficacy and safety outcomes from a follow-up single-arm, open-label, randomized, active-controlled phase 3 trial have been reported. Keynote-775 / Study 309 (N= 827) compared efficacy and safety of the combination therapy with lenvatinib (Lenvima) and pembrolizumab (LEN+Pembro), with a treatment of physician's choice (TPC; doxorubicin or paclitaxel) via a 1:1 randomization. Randomization was further stratified by DNA mismatch repair (MMR) status (i.e., pMMR versus dMMR) and microsatellite stability (MSI-H versus MSS). Primary efficacy outcomes were PFS and OS. All participants had prior progression on or after a platinum-based chemotherapy and no previous exposure to PD-1/ PD-L1 therapy. At median 12.2 months of follow-up, PFS was significantly improved with LEN + pembro versus TPC in pMMR advanced EC (median 6.6 vs 3.8 months: HR 0.60). OS in this population subset was significantly longer with LEN + pembro versus TPC (median 17.4 vs 12.0 months; HR 0.68). Additionally, efficacy outcomes in the overall trial population (both pMMR and dMMR EC) also favored LEN+ Pembro over TPC [median OS 18.3 vs 11.4 months (HR 0.62) and median PFS 7.2 vs 3.8 months (HR 0.56)]. However, given the majority participants in this clinical trial had MSS/pMMR EC (n=697 out of 827), the FDA approval is limited to the treatment of MSS/pMMR EC.

IX. **Desmoid Tumors (DT):**

- Desmoid tumors (DT) are rare, noncancerous growths, that are unable to metastasize and occur as a result of mutations in fibroblasts of connective tissue. DT can arise anywhere in the body, but most commonly appear in the abdominal/intra-abdominal area. The clinical course is variable, often with an initial growth phase followed by long periods of arrest and regression. Symptoms commonly include pain, fatigue, deformity, and functional impairment. Although non-malignant, DT can progress in size if left untreated and increase the risk of invasion into local organs.
- Sorafenib (Nexavar) for the treatment of DT was studied in one Phase 3, double-blind, placebo-controlled trial. Eligible patients were required to have newly diagnosed DT, or progressive DT and either had not received previous treatment for progressing DT that were not amenable to surgery or had refractory or recurrent DT after at least one line of

therapy. Median subject age was 37 years, majority female (69%), and extra-abdominal tumor-location (57%). Fifty four percent of the subjects in the sorafenib (Nexavar) group were newly diagnosed with DT, while the remaining 46% had recurrent disease after at least one form of previous treatment. The treatment experienced sorafenib (Nexavar) group treatments included surgery (46%), radiation therapy (12%), and systemic therapy (36%). The primary outcome was progression-free survival (PFS). Secondary endpoints included objective response rate (ORR) and overall survival (OS). Results showed a statistically significant 87% reduction of disease risk progression in subjects who received sorafenib (Nexavar) versus subjects who received placebo (hazard ratio [HR] = 0.13; $p < 0.001$).

- A definitive diagnosis of DT requires histopathologic analysis of a biopsy sample of the tumor which is examined for presence of desmoid cells. Both DTWG (2020) and NCCN soft tissue sarcoma (2023) guidelines recommend a histological diagnosis of DT via an image-guided (CT or ultrasound) core needle or surgical biopsy of the tumor site. Due to rarity of disease and association with other germline mutation syndromes (i.e., familial adenomatous polyposis [FAP], Gardner syndrome), it is essential to rule out potential for differential diagnosis without association to desmoid tumors (e.g., Gardner syndrome). DT also shares similarities with other myofibroblastic diseases (e.g., sarcoma, gastrointestinal stromal tumor, nodular fasciitis, leiomyoma) with 30% to 40% of DT cases reported to be misdiagnosed following histologic analysis. NCCN guidelines recommend evaluation and treatment by a multidisciplinary team with expertise and experience in desmoid tumors; however, DTWG guidelines require confirmation of diagnosis by a soft tissue pathologist.
- Both DTWG (2020) and NCCN (V 2.2023) guidelines recommend active surveillance/observation alone until the tumor has shown progression and is accompanied by significant symptom burden, at which point, active treatment is pursued. NCCN guidelines also recommend active treatment if progression of DT is accompanied by potential for morbidity. Guidelines recommend earlier active treatment in the case of nonprogressive DT in anatomical locations where progression of the tumor would be morbid. The Phase 3, placebo-controlled study included patients with either newly diagnosed or progressing desmoid tumors within 6 months of registration. Inclusion criteria encompassed patients who had symptomatic, progressive, or morbid disease unresectable to surgery. There is currently sufficient evidence to support the use of sorafenib (Nexavar) in subjects with nonprogressive DT.
- The use of sorafenib (Nexavar) has not been studied in combination with other chemotherapy agents (e.g., methotrexate and vinorelbine) or tyrosine kinase inhibitors (TKI's) such as pazopanib for use in desmoid tumors. Due to the lack of safety and efficacy data with a combination regimen, use of sorafenib (Nexavar) is not recommend with any other oncology therapy for the management of desmoid tumors.

Investigational or Not Medically Necessary Uses

- I. Lenvatinib (Lenvima), pazopanib (Votrient), sorafenib (Nexavar) have not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Gastrointestinal Stromal Tumor
 - B. Adipocytic Sarcoma/Liposarcoma

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- i. Pazopanib (Votrient) was studied as a targeted therapy option for the treatment of advanced Soft Tissue Sarcoma (STS) in one randomized, double-blind, placebo-controlled, multicenter, Phase 3 trial (N=369). Enrolled patients had metastatic STS who had failed at least one anthracycline-based chemotherapy regimen. Although patients with most histological subtypes of STS were included in this trial, patients with gastrointestinal stromal tumors (GIST) and adipocyte tumors (liposarcoma) were excluded.
- C. Sorafenib (Nexavar) in combination with erlotinib for Hepatocellular Carcinoma
 - i. Sorafenib (Nexavar) in combination with erlotinib, was studied in a randomized, placebo-controlled, Phase 3 trial in 720 patients with advanced HCC. Results found that the combination did not significantly improve survival relative to sorafenib (Nexavar) in combination with placebo. The combination had a significantly lower disease control rate (p=0.021) and a shorter treatment duration of 86 days compared to 123 days for sorafenib/erlotinib and sorafenib/placebo, respectively.

** 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. Lenvima [Prescribing Information]. Woodcliff Lake, NJ: Eisai, Inc. July 2021.
2. Votrient [Prescribing Information]. East Hanover, NJ: Novartis Pharmaceuticals. August 2020.
3. Nexavar [Prescribing Information]. Whippany, NJ: Bayer Healthcare Pharmaceuticals, Inc. July 2020.
4. Motzer R, Alekseev B, et al. Lenvatinib plus Pembrolizumab or Everolimus for Advanced Renal Cell Carcinoma. *N Engl J Med*. 2021 Apr 8;384(14):1289-1300.
5. Makker V, Rasco D et al. Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer: an interim analysis of a multicenter, open-label, single-arm, phase 2 trial. *Lancet Oncol*. 2019 May;20(5):711-718.
6. Gilbert JA. Pazopanib for advanced liposarcoma. *Lancet Oncol*. 2017 Oct;18(10): e564. doi: 10.1016/S1470-2045(17)30663-0.
7. Chamberlain FE, et al. Pazopanib in patients with advanced intermediate-grade or high-grade liposarcoma. *Expert Opin Investig Drugs*. 2019 Jun;28(6):505-511.
8. Olivier Mir MD et al. PAZOGIST trial, *Lancet Oncology*; 2016; 17 (55) 632-641.
9. National Comprehensive Cancer Network. NCCN Guidelines: Soft Tissue Sarcoma. Version 2.2021. Updated April 28, 2021.
10. National Comprehensive Cancer Network. NCCN Guidelines: Kidney Cancer. Version 1.2022. Updated July 1, 2021.
11. National Comprehensive Cancer Network. NCCN Guidelines: Hepatobiliary Cancers. Version 3.2021. Updated June 15, 2021.
12. National Comprehensive Cancer Network. NCCN Guidelines: Thyroid Carcinoma. Version 1.2021. Updated April 9, 2021.
13. National Comprehensive Cancer Network. NCCN Guidelines: Uterine Neoplasms. Version 3.2021. Updated June 6, 2021.
14. Gounder MM, Mahoney MR, et al. Sorafenib for Advanced and Refractory Desmoid Tumors. *N Engl J Med*. 2018 Dec 20;379(25):2417-2428.
15. Makker V, Taylor MH, et al. Lenvatinib Plus Pembrolizumab in Patients With Advanced Endometrial Cancer. *J Clin Oncol*. 2020 Sep 10;38(26):2981-2992.
16. Makker V et al. 2021; A multicenter, open-label, randomized, phase III study to compare the efficacy and safety of lenvatinib in combination with pembrolizumab versus treatment of physician's choice in patients with advanced

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endometrial cancer; Soc. Gyn. Oncol. SGO2021 Virtual Annual Meeting on Women's Cancers; mar 19 2021; abstract 11512; https://157slyoyo4y17zpa538hczs1-wpengine.netdna-ssl.com/wp-content/uploads/2021/01/FRIDAY_2021-Virtual-Annual-Meeting-on-Womens-Cancer.pdf

17. National Comprehensive Cancer Network. Soft Tissue Sarcoma (Version 3.2023). NCCN. Updated December 12, 2023. Accessed December 18, 2023. https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf
18. Desmoid Tumor Working Group. The management of desmoid tumours: A joint global consensus-based guideline approach for adult and paediatric patients. Eur J Cancer. 2020;127:96-107. doi:10.1016/j.ejca.2019.11.013

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
cabozantinib (Cabometyx)	Differentiated Thyroid Carcinoma (DTC)
	Renal Cell Carcinoma (RCC)
	Hepatocellular Carcinoma (HCC)
everolimus (Afinitor, Afinitor Disperz)	Angiomyolipoma of the kidney, tuberous sclerosis syndrome
	Breast cancer, advanced, HR+, HER2 -, in combination with exemestane after failure with letrozole or anastrozole
	Neuroendocrine tumor, gastrointestinal, lung or pancreatic, unresectable locally advanced or metastatic
	Renal Cell Carcinoma (RCC)
	Subependymal giant cell astrocytoma
	Partial seizure, adjunct, tuberous sclerosis syndrome
fedratinib (Inrebic®) Policy	Myelofibrosis
nirogacestat (Ogsiveo™) Policy	Desmoid tumors
regorafenib (Stivarga)	Colorectal Cancer
	Gastrointestinal Stromal Tumor
	Hepatocellular Carcinoma
vandetanib (Caprelsa)	Locally advanced or metastatic medullary thyroid cancer
sunitinib (Sutent)	Gastrointestinal stromal tumor
	Renal Cell Carcinoma (RCC)
	Neuroendocrine pancreatic tumor

Policy Implementation/Update:

Action and Summary of Changes	Date
Added requirement to trial generic pazopanib prior to branded Votrient	11/2023
Added desmoid tumors as a covered indication to generic and brand sorafenib (Nexavar)	02/2024
Added requirement to trial generic pazopanib prior to branded Votrient	11/2023
Added requirement to trial generic sorafenib tosylate prior to branded Nexavar	06/2022
Rearranged and updated Lenvima dosing and quantity limits based on recommended maximum dose for each indication; QL exceptions would be allowed only for dose reductions	02/2022
Moved "Sorafenib (Nexavar) for the treatment of desmoid tumors (aggressive fibromatosis)" out of the "Not Medically Necessary" section to "Investigational Use" section; Changed policy name from "Lenvatinib (Lenvima™), pazopanib (Votrient®), sorafenib (Nexavar®)" to "Multi-Targeted Tyrosine Kinase Inhibitors (Multi-TKI)"	10/2021
Updated policy to include Lenvima and pembrolizumab combination therapy for endometrial carcinoma and as first-line therapy for RCC; In the HCC setting: removed criteria requiring member being treatment-naïve allowing coverage in first-line as well as 2 nd -line settings, added requirement for Child-Pugh class A/B7. Updates to supporting evidence sections.	09/2021

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Added clinical trial data for sorafenib (Nexavar) in the setting of desmoid tumors to the supporting evidence (investigational and not medically necessary uses: C.ii)	04/2021
Updated supporting evidence for investigational indication of endometrial carcinoma for Lenvima	12/2020
Transitioned criteria to policy format and merged into one policy; Updated criteria to include lenvatinib (Lenvima) requires failure of at least one anti-angiogenic therapy and combination therapy of lenvatinib (Lenvima) with everolimus (Afinitor); Updated disease staging requirements for most indications; Updated information on endometrial cancer for lenvatinib (Lenvima); Updated supporting evidence section	10/2020
Previous reviews • Lenvima: Updated indication to include advanced renal cell carcinoma (2017), updated indication to include unresectable hepatocellular carcinoma (2018) • Votrient: Updated to reflect FDA approved indications and quantity limits (2016) • Nexavar: Updated to reflect FDA approved indications (2016)	10/2018, 06/2017, 03/2016, 03/2016
Criteria created • Lenvima: 2015 • Votrient: 2012 • Nexavar: 2012	03/2015 02/2012 03/2012

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP295

Description

Nedosiran (Rivfloza) is a subcutaneously injected *LDHA*-directed small interfering RNA indicated to lower urinary oxalate levels in those with primary hyperoxaluria type 1 (PH1).

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
nedosiran (Rivfloza)	Primary hyperoxaluria type 1 (PH1) with relatively preserved kidney function (e.g., eGFR $\geq$ 30 mL/min/1.73 m ²)	80mg vial*	2 vials/28 days
		128mg pre-filled syringe*	1 pre-filled syringe/28 days
		160mg pre-filled syringe*	

*Dosing is based on member's weight. Please see appendix.

Initial Evaluation

- I. **Nedosiran (Rivfloza)** may be considered medically necessary when the following criteria are met:
 - A. Member is 2 years of age or older; **AND**
 - B. Documentation of member's weight; **AND**
 - C. Medication is prescribed by, or in consultation with, a nephrologist, urologist, or medical geneticist; **AND**
 - D. Medication will not be used in combination with lumasiran (Oxlumo); **AND**
 - E. A diagnosis of **primary hyperoxaluria type 1 (PH1)** when the following are met:
 1. Diagnosis of PH1 confirmed with alanine glyoxylate aminotransferase (AGXT) mutation via genetic testing or liver enzyme analysis; **AND**
 2. Member has not undergone a liver transplant; **AND**
 3. Provider attestation that the member has an eGFR $\geq$ 30mL/min/1.73m²; **AND**
 4. Documentation of baseline for one or more of the following:
 - i. Urinary oxalate excretion level (corrected for BSA)
 - ii. Spot urinary oxalate: creatinine ratio
 - iii. Estimated glomerular filtration rate (eGFR)
 - iv. Plasma oxalate level; **AND**
 5. Medication will be used in combination with pyridoxine; **OR**
 - i. Member has been classified as a non-responder to pyridoxine after a three-month trial
- II. Nedosiran (Rivfloza) is considered investigational when used for all other conditions, including but not limited to:

- A. Primary hyperoxaluria type 2 (PH2)
- B. Primary hyperoxaluria type 3 (PH3)
- C. When used in combination with lumasiran (Oxlumo)

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; **AND**
- IV. Medication will not be used in combination with lumasiran (Oxlumo); **AND**
- V. Member has not undergone a liver transplant; **AND**
- VI. Attestation member has an eGFR $\geq 30 \text{ mL/min/1.73 m}^2$; **AND**
- VII. Member has exhibited improvement or stability of disease symptoms as evidenced by at least one of the following:
 - A. Decrease in urinary oxalate excretion from baseline
 - B. Reduction in spot urinary oxalate: creatinine ratio from baseline
 - C. Stabilization of glomerular filtration rate
 - D. Decrease in plasma oxalate level from baseline; **AND**
- VIII. Medication will be used in combination with pyridoxine; **OR**
 - A. Member has been classified as a non-responder to pyridoxine after a three-month trial

Supporting Evidence

- I. Nedosiran (Rivfloza) is a *LDHA*-directed small interfering RNA, FDA-approved to lower urinary oxalate levels in those two years of age and older with primary hyperoxaluria type 1 (PH1) and relatively preserved kidney function (e.g., eGFR $\geq 30 \text{ mL/min/1.73 m}^2$). The efficacy and safety of nedosiran (Rivfloza) has not been established in patients under the age of two. Dosing of nedosiran (Rivfloza) is based on actual body weight.
- II. Primary hyperoxaluria (PH) is a group of autosomal recessive disorders of hepatic glyoxylate metabolism that cause the overproduction of endogenous oxalate — a redundant metabolic end product that is excreted primarily via the kidneys. Primary hyperoxaluria type 1 (PH1) is the most common and severe type of PH, due to mutations of the *AGXT* gene. Variants of this gene result in enhanced oxalate production. In high levels, oxalate forms crystals which can deposit in various parts of the body. As oxalate is typically excreted in the urine, the kidney is the prime target for oxalate deposition resulting in nephrocalcinosis, kidney stones, and end-stage kidney disease (ESKD). Some patients progress to systemic oxalosis when the GFR falls <30 to $40 \text{ mL/min per } 1.73 \text{ m}^2$ which results in calcium oxalate deposits in the heart, blood vessels, joints, bones, and retinas.
- III. PH1, which accounts for approximately 80% of PH cases, has an estimated prevalence of one to three per million in Europe and North America. Age at diagnosis varies, with some not being diagnosed until adulthood, and the median age at diagnosis is 5 years old. Those with more

severe disease present earlier in life with a diagnosis in infancy, accounting for approximately 26% of patients.

- IV. Given the complexities related to diagnosis, treatment, and management of PH1, treatment in this disease space must be initiated by, or in consultation with, a specialist (e.g., nephrologist, urologist, or medical geneticist).
- V. Nedosiran (Rivfloza) was studied in a Phase 2, multinational, double-blind, placebo-controlled trial (PHYOX2) of 35 patients with genetically confirmed PH1 (n=29) or PH2 (n=6). Participants also had to have a 24-hour urinary oxalate (Uox) excretion of ≥ 0.7 mmol and an estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m². Patients were randomized 2:1 to receive nedosiran (Rivfloza) or placebo. All participants were instructed to continue their standard of care (conservative) therapies. Median age: 20 years (range: 9–46 years), 51% female, 71% White, 17% Asian. Baseline demographic and disease characteristics were generally balanced between the two treatment arms, with the exception of 24-hour Uox excretion at baseline, which was higher in the placebo arm (1.33 vs 1.96 mmol/24 hr). The primary efficacy outcome was the percent change from baseline in 24-hour Uox excretion, as assessed by area under the curve (AUC) from day 90 to day 180. Key secondary endpoints included the proportion of participants reaching normal or near-normal 24-hour Uox excretion on at least two consecutive visits, starting at day 90.
- VI. The least-squares (LS) mean AUC 24-hour Uox was -3486 (95% CI: -5025, -1947) in the nedosiran (Rivfloza) group compared to 1490 (95% CI: 781, 3761) in the placebo group; a between group difference of 4976 (95% CI: 2803, 7149; $p < 0.0001$) was detected. The LS mean percent change from baseline in 24-hour urinary oxalate excretion (corrected for BSA in patients <18 years of age) averaged over Days 90, 120, 150 and 180, was -37% (95% CI: -53%, -21%) in the nedosiran (Rivfloza) group and 12% (95% CI: -12%, 36%) in the placebo group, for a between group difference of 49% (95% CI: 26%, 72%). Among patients with PH1, the between group difference was 56% (95% CI: 33%, 80%).
- VII. While nedosiran (Rivfloza) demonstrated statistically significant results for the primary endpoint and this surrogate endpoint is accepted as a clinically meaningful endpoint by the FDA, the magnitude of AUC reduction correlating to a clinically significant impact is unclear at this time. The key secondary endpoint was only achieved in 48% of patients and was driven by patients who achieved a near-normalized 24-hour Uox, rather than those with normalized 24-hour Uox. Additionally, the secondary endpoint results may be difficult to reconcile as baseline characteristics between the treatment groups were unbalanced, and results may favor the study drug. Therefore, the quality of evidence is considered low.
- VIII. Nedosiran (Rivfloza) was studied in a phase 2, multi-dose, open-label, single-arm, uncontrolled, multicenter trial of 21 pediatric patients (ages 0-11) with genetically confirmed PH1 (n=15) and relatively preserved kidney function. Inclusion required an average spot Uox:Ucr ratio $> 2 \times$ the 95th percentile for age and an estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m² (or normal serum creatinine for participants less than 12 months of age). All participants were instructed to continue their standard of care (conservative) therapies. Median age: 5.0 years (range: 2-11), 33.3% female, 66.7% male, 80% white. Most patients had CKD stage 1 or 2 (80%), with 6.7% in stage 3A and 13.3% in stage 3B. Participants were grouped by age: 2 to <6 years (n=8), 6 to <9 years (n=5), 9 to 11 years (n=2) for subgroup analysis. Baseline disease characteristics (e.g., eGFR, plasma oxalate, time since diagnosis, number of kidney stone events

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in the last 12 months, CKD stage, and urinary oxalate) varied across prespecified age groups, though outcomes were consistent at study end. The primary efficacy endpoint was the percent change in spot Uox:Ucr ratio from baseline. Key secondary endpoints include percentage of participants with spot Uox:Ucr ratio $\leq 1.0 \times \text{ULN}$ or $\leq 1.5 \times \text{ULN}$ at any time point, change in eGFR, and safety.

- IX. The least-squares (LS) mean percent change from baseline in Uox:Ucr was -56.4% (95% CI: $-70.7, -42.1$) including all participants, and -68.5% (95% CI: $-83.1, -53.9$) in a sensitivity analysis excluding one ineligible participant. Reduction in Uox:Ucr was comparable between the different age groups by day 180. At any time point, 93.3% of participants ($n=14$) achieved Uox:Ucr $< 1.5 \times \text{ULN}$, and 53.3% ($n=8$) achieved normalization ($\leq 1.0 \times \text{ULN}$). The LS median percent change in eGFR was 2.5%, indicating preserved renal function over the trial period. No adverse events (AEs) led to treatment interruption or discontinuation. Three participants (20%) experienced at least one serious adverse event (SAE), but none were considered treatment related. The most common AEs were injection site reactions (6.7%, all grade 1) and mild kidney stone-related events (26.7%). No patients reported muscle-related AEs.
- X. The PHYOX8 study carries a high risk of bias and low confidence due to its open-label, single-arm design and small sample size, but it remains the only available clinical trial evaluating the efficacy and safety of nedosiran (Rivfloza) in the expanded pediatric age group. The efficacy and safety outcomes are consistent with previous pivotal PHYOX trials, supporting the validity of findings. While long-term outcome data and generalizability remain uncertain, the data are reasonable to inform use of therapy for the expanded indication in the absence of alternative evidence.
- XI. Per the clinical practice recommendations for primary hyperoxaluria genetic testing is the gold standard for the diagnosis of all three types of PH. The consensus statement recommends that all patients who are suspected to have PH should undergo genetic assessment, as genetic confirmation of PH and typing are pivotal to the management of these patients. PH1 is due to mutations of the AGXT gene. Whereas PH2 is due to a deficiency in glyoxylate and hydroxypyruvate reductase (GRHPR) and PH3 is due to the loss of function of the mitochondrial enzyme 4-hydroxy-2-oxoglutarate adolase (HOGA). Biochemical assessment has an important role in the diagnostic workup of patients with symptoms suggestive of PH and can focus genetic testing. It can also be used as an indication of therapeutic response. However, measurement of oxalate and relevant metabolites is not without difficulty, and one must interpret the results carefully, taking all potential flaws into account.
- XII. Liver transplantation is the only curative intervention for PH1 as it corrects the underlying enzymatic defect due to mutations of the AGXT gene. Use and efficacy of nedosiran (Rivfloza) after transplant has not been evaluated in clinical trials.
- IX. While the primary endpoint in clinical trials was 24-hour urinary oxalate excretion, it may be difficult for some patients to obtain a 24-hour urine collection in clinical practice. This can especially be noted in infants and small children who are not toilet trained, working adults, and school aged children. As a result, oxalate excretion can be evaluated by measuring the molar oxalate:creatinine ratio in spot urine samples. A 24-hour oxalate excretion does not correlate perfectly with oxalate-to-creatinine ratio, possibly as a consequence of imperfect urine collections and the effect of body size, which influences creatinine excretion and may therefore affect the oxalate-to-creatinine ratio. However, available evidence suggests that either

measurement can be used to monitor response to treatment. Plasma oxalate can be a useful biomarker in PH1 as urinary oxalate measurements may be falsely low in patients with kidney insufficiency and progressive disease, which is common in patients with type 1 disease. In this setting, plasma oxalate levels may be useful, as there is an inverse relation between plasma oxalate and kidney function in children with early stages of chronic kidney disease where oxalate excretion has declined to such an extent that urine results are misleading. Lastly, estimated glomerular filtration rate can help to assess progression in ESKD in PH1 patients.

- X. The efficacy and stability of symptoms can be assessed by multiple surrogate endpoints as compared to baseline (i.e., a decrease in urinary oxalate excretion from baseline, reduction in spot urinary oxalate: creatinine ratio from baseline, stabilization of glomerular filtration rate, decrease in plasma oxalate level from baseline). Therefore, improvement or stability in one metric provides enough evidence to support continuation of therapy.
- XIII. Aside from drug therapies general measures used in all patients with PH1 include: hyperhydration, citrate and magnesium supplements to increase urinary oxalate solubility, and pyridoxine (vitamin B6). Pyridoxine is variably effective in some genotypes and is trialed for three to 6 months to see if the patient is a responder. Liver transplant is curative as it corrects the mutation in the AGXT gene but is associated with significant morbidity. Some patients may undergo sequential or isolated liver-kidney transplants.
- XIV. Nedosiran (Rivfloza) can be self-administered or caregiver-administered at home via a single-dose prefilled syringe or vial.

Investigational or Not Medically Necessary Uses

- I. Nedosiran (Rivfloza) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Primary hyperoxaluria type 2 (PH2)
 - i. Only six patients diagnosed with PH2 were included in the nedosiran (Rivfloza) pivotal trial (PHYOX2). There was no consistent pattern observed for 24-hour Uox excretion in treated or untreated PH2 participants, thus the safety and efficacy of nedosiran (Rivfloza) in PH2 remains investigational.
 - B. Primary hyperoxaluria type 3 (PH3)
 - i. Nedosiran (Rivfloza) has not been FDA-approved or sufficiently studied for safety and efficacy for PH3.
 - C. When used in combination with lumasiran (Oxlumo)
 - i. On November 23, 2020, FDA approved lumasiran (Oxlumo) to lower urinary oxalate levels, a surrogate for kidney stones and loss of kidney function, in pediatric and adult patients with PH1 who have relatively preserved kidney function. Lumasiran (Oxlumo) is a small interfering ribonucleic acid (siRNA) that reduces levels of the glycolate oxidase enzyme by targeting the hydroxyacid oxidase 1 (HAO1) messenger ribonucleic acid (mRNA) in hepatocytes. On October 6, 2022, lumasiran (Oxlumo) was also approved to lower plasma oxalate, a surrogate for systemic manifestations of PH1, in patients with more advanced kidney disease. While both lumasiran (Oxlumo) and nedosiran (Rivfloza) are siRNA therapies approved for the treatment of PH1, their concurrent use has not been evaluated for safety or efficacy.

Appendix

Table 1: FDA approved dosing

Age	Body Weight	Dosing Regimen
Adults and adolescents 12 years and older	≥ 50 kg	160 mg once monthly (Pre-filled Syringe, 1mL)
	< 50 kg	128 mg once monthly (Pre-filled Syringe, 0.8mL)
Age 2 to less than 12 years	≥ 50 kg	160 mg once monthly (Pre-filled Syringe, 1mL)
	39 kg to <50 kg	128 mg once monthly (Pre-filled Syringe, 0.8 mL)
	<39 kg	3.3 mg/kg once monthly, not to exceed 128 mg (Vial, 0.5 mL)

References

1. Rivfloza. Package Insert. Novo Nordisk Inc; March 2025.
2. Baum MA, Langman C, Cochat P, et al. PHYOX2: a pivotal randomized study of nedosiran in primary hyperoxaluria type 1 or 2. *Kidney Int.* 2023;103(1):207-217.
3. Sas DJ, Bakkaloglu SA, Belostotsky V, et al. Nedosiran in pediatric patients with PH1 and relatively preserved kidney function, a phase 2 study (PHYOX8). *Pediatr Nephrol.* 2025;40(6):1939-1948.
4. Groothoff JW, Metry E, Deesker L, et al. Clinical practice recommendations for primary hyperoxaluria: an expert consensus statement from ERKNet and OxalEurope. *Nat Rev Nephrol.* 2023;19(3):194-211.

Related Policies

Currently there are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated age criteria and dosing to reflect newly FDA approved age expansion from 9 years of age to 2 years of age. Updated supporting evidence and references.	08/2025
Policy created.	02/2024

Policy Type: PA/SSP

Pharmacy Coverage Policy: UMP312

Description

Nemolizumab (Nemluvio) is an interleukin-31 (IL-31) receptor alpha antagonist.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
nemolizumab (Nemluvio)	Prurigo Nodularis	30 mg prefilled pen	First month: 2 (30mg) prefilled pens/28 days Maintenance: • Under 90kg: 1 (30mg) prefilled pen/28 days • 90kg or more: 2 (30mg) prefilled pens/28 days
	Atopic Dermatitis		First month: 2 (30mg) prefilled pens/28 days Maintenance: 1 (30mg) prefilled pen/28 days

Initial Evaluation

- I. **Nemolizumab (Nemluvio)** 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 will not be used in combination with another biologic for the treatment of prurigo nodularis or atopic dermatitis [e.g., dupilumab (Dupixent), upadacitinib (Rinvoq)]; **AND**
 - C. A diagnosis of **prurigo nodularis (PN)** when the following are met:
 1. Member is 18 years of age or older; **AND**
 2. Member has a confirmed diagnosis of moderate to severe prurigo nodularis based on all of the following:
 - i. Presence of nodules for at least 3 months; **AND**
 - ii. Disease is moderate to severe in severity (e.g., Peak Pruritis Numeric Rating Scale (PP-NRS) score of at least 7; Investigator Global Assessment (IGA) score of 3 or 4; presence of at least 20 lesions on the body); **AND**
 - iii. Provider attests the underlying cause of prurigo nodularis (PN) is not considered to be drug-induced or caused by other medical conditions, such as dermatillomania; **AND**

3. Treatment with at least one medium to very high potency topical corticosteroid has been ineffective, not tolerated, or contraindicated; **AND**
 4. Treatment with at least one of the following has been ineffective or not tolerated, unless all are contraindicated:
 - i. Topical calcineurin inhibitors (e.g., pimecrolimus cream, tacrolimus ointment)
 - ii. Topical vitamin D analogue (e.g., calcipotriene)
 - iii. Phototherapy (UVA or PUVB)
 - iv. Systemic immunosuppressants (e.g. methotrexate or cyclosporine); **AND**
 5. Treatment with dupilumab (Dupixent) has been ineffective, contraindicated, or not tolerated; **OR**
- D. A diagnosis of **atopic dermatitis (AD)** when the following are met:
1. Member is 12 years of age or older; **AND**
 2. Body surface area (BSA) involvement of at least 10%; **OR**
 - i. Involves areas of the face, ears, hands, feet, or genitalia; **AND**
 3. Treatment with at least two of the following groups has been ineffective or not tolerated, unless 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. pimecrolimus cream, tacrolimus ointment)
 - iii. Group 3: Branded topical agents crisaborole (Eucrisa) or ruxolitinib (Opzelura); **AND**
 4. Treatment with dupilumab (Dupixent) or upadacitinib (Rinvoq) have been ineffective, contraindicated, or not tolerated; **AND**
 5. Medication will be used in combination with topical corticosteroids and/or calcineurin inhibitors unless both are contraindicated
- II. Nemolizumab (Nemluvio) is considered investigational when used for all other conditions, including but not limited to:
- A. Chronic Kidney Disease with associated moderate to severe pruritis
 - B. Systemic Sclerosis

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 another biologic (e.g., dupilumab [Dupixent]) or Janus Kinase inhibitor (e.g., upadacitinib [Rinvoq]); **AND**
- IV. Member has exhibited improvement or stability of disease symptoms for the following:

- For Prurigo Nodularis (PN): clearance of the skin as determined by Investigator Global Assessment (IGA) score of 0 or 1, reduced prurigo nodularis (PN) nodules, reduction in score on the Peak Pruritis Numeric Rating Scale (PP-NRS) scale
- For Atopic Dermatitis (AD): clearance of the skin as determined by Investigator Global Assessment (IGA) score of 0 or 1, improvement in the Eczema Area and Severity Index-75

Supporting Evidence

- I. Nemolizumab (Nemluvio) is FDA approved for the treatment of prurigo nodularis in adult patients. It is pending FDA approval in December 2024 for atopic dermatitis. The safety and efficacy in other disease states is unknown.
- II. Due to the complexity of diagnosis and treatment, nemolizumab (Nemluvio) should be prescribed by, or in consultation with a dermatologist.

Prurigo Nodularis

- I. Prurigo nodularis (PN) is a distinct dermatological condition defined by the presence of chronic pruritis and multiple localized or generalized, elevated, firm, and nodular lesions. The exact underlying cause of PN is unknown, neural and immunologic processes both appear to play a role in its development. Prurigo nodularis (PN) is more common in women, older adults, and African Americans. The disease may arise without any other secondary dermatologic diagnosis, such as atopic dermatitis. Prurigo nodularis (PN) is associated with the severest itch of the various skin conditions as well as significant disease burden, including sleep disruption, anxiety, and depression. Prurigo nodularis (PN) is perpetuated by the sensitization induced by the scratch-itch cycle and treating any underlying cause alone may not provide sufficient relief.
- II. Although literature suggests up to 60% of patients with PN have a history of atopic conditions (atopic dermatitis, allergic rhinitis, asthma, etc.), both drugs induced PN (e.g., opioids, ACE inhibitors, etc.) or PN due to other medical conditions such as neuropathy or psychiatric disease (i.e. dermatillomania, obsessive compulsive disorder, etc.), should be considered and ruled out in the making of a diagnosis of PN. Additionally, short-term lesions, under three months, should also be ruled out for other dermatologic conditions, such as lichen planus. The American Academy of Dermatology (AAD) 2021 guidelines on the diagnosis of management of prurigo nodularis, outline traditional therapies used for PN before biologic therapy, such as dupilumab (Dupixent) or nemolizumab (Nemluvio), were approved. Treatment consists of moderate to very high potency topical steroids (TCS), including intralesional injections, topical calcineurin inhibitors, capsaicin, narrowband ultraviolet (UVB) phototherapy, as well as systemic therapies. Systemic options include oral immunosuppressants, such as low dose methotrexate, cyclosporine, as well as neuromodulators (e.g., gabapentinoids, cannabinoids), antihistamines, and antidepressants (e.g., amitriptyline, doxepin).
- III. Safety and efficacy of nemolizumab (Nemluvio) was studied in two similarly designed Phase 3, double-blind, multicenter, placebo-controlled trials (OLYMPIA 1 and 2). Five hundred and sixty total adult patients, mainly white and diagnosed with prurigo nodularis for at least six months, were randomized 2:1 to receive either nemolizumab (Nemluvio) at 30 mg or 60 mg monthly versus matching placebo. Patients had prior use of topical therapies in 78% in the nemolizumab (Nemluvio) arm and 72% in placebo, with prior systemic therapies of 57% and 62% respectively. Most patients at baseline were on topical steroids (78%) with either antihistamine use (39%), another topical agent (22%), or immunosuppressants (19%); though use was not allowed during the trial period. At baseline, 65% of patients had 20-100 nodules over their body, an average

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Peak Pruritis Numeric Rating Scale (PP-NRS) of 8.5, 58% had Investigator's Global Assessment (IGA) score of 3 (moderate PN), and 42% had IGA score of 4 (severe PN). The co-primary endpoints assessed improvement in skin lesions and pruritis from baseline to Week 16 using PP-NRS and IGA scales.

- IV. Investigator global assessment (IGA) score is a five-point scale rating from 0 (clear, no nodules) to 4 (severe, ≥ 100 nodules) done by providers to assess disease severity. The peak pruritis numeric rating scale (PP-NRS) is an 11-point scale from 0 (no itch) to 10 (worst itch imaginable) that asks the patient to rate itch at the worst moment during the previous 24 hours, it is interchangeable with the worst itch numeric rating scale. The PP-NRS score is a validated endpoint with a clinical meaningful change seen by improvement of four points. Patients in OLYMPIA 1 and 2 all had an IGA score of 3 or 4 (moderate to severe skin involvement) and a PP-NRS score of ≥ 7 (severe itch).
- V. Both primary endpoints in OLYMPIA 1 and 2 were met:
 - OLYMPIA 1: A significantly greater improvement in itch intensity and skin lesions with nemolizumab (Nemluvio) treatment was observed at week 16 compared to placebo. There were 58.4% of subjects treated with nemolizumab (Nemluvio) who had a ≥ 4 -point improvement in weekly average PP-NRS score from baseline compared to 16.7% in placebo group ($P < 0.0001$). There were 26.3% of nemolizumab (Nemluvio)-treated subjects achieving IGA success, as defined by an IGA response of 0 (clear) or 1 (almost clear) and a ≥ 2 -point reduction from baseline, compared to 7.3% in placebo group ($P = 0.0025$).
 - OLYMPIA 2: A greater proportion of patients achieving an improvement in PP-NRS by four or more points and obtaining an IGA score of 0 or 1 on nemolizumab (Nemluvio) ($n=183$) versus placebo ($n=91$). PP-NRS: 103 versus 19 patients, treatment difference of 37.4 (26.3-48.5, $P<0.001$) and IGA: 69 versus 10 patients, treatment difference of 28.5 (18.8-38.2 $P<0.001$).
- VI. Key secondary endpoints such as the number of patients reaching the PP-NRS reduction by week four and improvement in the sleep disturbance numerical rating scale also reached statistically significant differences in both clinical trials with an average 30% more patients achieving improvement in both clinical trial endpoints.

Atopic Dermatitis

- I. Atopic dermatitis (AD) is a common, chronic, flaring inflammatory skin disease affecting millions of people worldwide. In the US, 31.6 million adults have moderate-to-severe AD, with symptoms of eczematous lesions, pruritis, and sleep disturbances. Treatments for mild-to-moderate atopic dermatitis 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 the 2024 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.
- II. 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 interleukin-13 antagonists (e.g., dupilumab, lebrikizumab,

tralokinumab) can be used. 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 months of age. Upadacitinib (Rinvoq), lebrikizumab (Ebglyss), tralokinumab (Adbry) have been evaluated and FDA approved in patients down to 12 years of age. Abrocitinib (Cibinqo) is FDA approved in adult patients only.

- III. 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% body surface area (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), severe limitation of everyday activities and psychosocial functioning, and 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.
- IV. Nemolizumab (Nemluvio) was studied in two identical, Phase 3, multicenter, randomized, placebo-controlled trials (ARCADIA 1 and 2). A total of 1,728 patients aged 12 years and older, with moderate to severe AD, not controlled by topical therapies alone, were randomized 2:1 to receive nemolizumab (Nemluvio) 30 mg monthly or matching placebo. Patients remained on background topical steroids (TCS) and topical calcineurin inhibitors (TCI), if applicable. At baseline, 71% of patients had an IGA score of 3 with an average eczema area and severity index score (EASI-75) of 27.3 affecting on average 19% of their body surface area (BSA). The change from baseline to week 16 in the IGA score and a 75% improvement in the EASI-75 were co-primary endpoints.
- V. Both co-primary endpoints were met in each trial:
 - Thirty-six percent and 38% of nemolizumab-treated patients in ARCADIA 1 and 2 achieved clear skin, defined by an investigator's global assessment score of clear (0) or almost-clear (1), when compared to the placebo group (25% and 26%, respectively; $p < 0.001$).
 - Forty-four percent and 42% of nemolizumab-treated patients in ARCADIA 1 and 2 achieved at least a 75% improvement in the eczema area and severity index score, when compared to the placebo group (29% and 30%, respectively; $p < 0.001$).
- VI. Key secondary endpoints, such as the number of patients reaching the PP-NRS reduction by week four and improvement in the sleep disturbance numerical rating scale, also reached statistically significant differences in both ARCADIA 1 and 2.

Evidence Summary

- I. Overall, the quality of evidence for nemolizumab (Nemluvio) is considered moderate. Well-designed Phase 3 trials in both PN and AD showed statistical significance in the co-primary endpoints as well as key secondary endpoints. For atopic dermatitis, these endpoints reflect skin improvement and less disease burden overall. For prurigo nodularis, these endpoints reflect marked clinically meaningful changes in reduction of itch as well as clearing PN nodules from the body. There was an underrepresented population in the African American enrollment for PN, which leads to uncertainty in the applicability in this population.

- II. The most common individual adverse events of both OLYMPIA trials (occurring in $\geq 5\%$ of the patients) that emerged during the treatment period in the nemolizumab (Nemluvio) group and were reported with higher frequency than in the placebo group were atopic dermatitis (5.5% versus zero) and headache (6.6 versus 4.4%). Overall, more adverse events occurred in the nemolizumab (Nemluvio) arms than the placebo arms in both OLYMPIA trials (66.5 versus 59.1%) and ARCADIA trials (45.5 versus 44.5%). The pooled adverse events of special interest that occurred more frequently in the nemolizumab (Nemluvio) groups than in the placebo groups were peripheral or facial edema and asthma; whereas infections were more common in the placebo groups than in the nemolizumab groups. The ARCADIA trial also had herpes zoster infections specifically associated with nemolizumab use. All peripheral or facial edema events were nonserious and were considered to be mild or moderate in severity.
- III. The use of nemolizumab (Nemluvio) over 30 mg monthly for AD has not been studied in the U.S. or approved by the FDA and requests for quantities over 30 mg monthly would be considered experimental. While nemolizumab (Nemluvio) has been studied as 60 mg monthly dose for the treatment of prurigo nodularis (PN), as well as approved in Japan as a 60 mg monthly dose for the use in AD, the up dosing remains experimental in this PN and is not supported by the FDA. When higher than the FDA approved dosing is requested, the use of other biologic therapies should be considered.
- IV. Nemolizumab (Nemluvio) for AD is approved for add-on to topical corticosteroids and/or calcineurin inhibitors and should be initiated on top of conventional therapies. Once the disease, has improved, topical therapies should be discontinued.

Investigational or Not Medically Necessary Uses

- I. Nemolizumab (Nemluvio) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Chronic Kidney Disease with associated moderate to severe pruritis
 - i. Clinical trial NCT05075408, NemoCKDaP, was a Phase II multicenter, double-blind, randomized, placebo-controlled trial over 12 weeks evaluating the efficacy and safety of nemolizumab versus placebo to reduce the intensity of pruritic in adult hemodialysis participants with moderate to severe pruritis. A total of 258 adult patients with end-stage kidney disease (ESKD) on hemodialysis three times per week for at least three months before the trial, pruritis for at least three months with a worse-itch numeric rating scale (WI-NRS) of five or better were enrolled and randomized. Patients were randomized to nemluvio (30 or 60mg monthly) versus placebo. The primary endpoint was the number of responders with an improvement in the WI-NRS by at least four points at the end of week 12. Results have not been published as of October 2024. All requests for this indication are considered experimental and investigational.
 - B. Systemic Sclerosis
 - i. Clinical trial NCT05214794, is an open-label, single-arm, Phase II study to assess efficacy and safety in patients with systemic sclerosis in Japan. Patients aged 20-70 years old, with diagnosis of systemic sclerosis (SSc) by the American college of Rheumatology (ACR) and European League Against Rheumatism (EULAR) 2013 criteria. All patients had moderate to severe skin sclerosis involvement and received nemolizumab. The change in baseline in the modified Rodnan Skin Score

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(mRSS) at week 24 was the primary endpoint at week 24. The modified Rodnan skin score (mRSS) is a measure of skin thickness and is used as a primary or secondary outcome measure in clinical trials of systemic sclerosis (scleroderma). It is a validated endpoint used as a surrogate for disease activity, severity and mortality in patients with dcSSc (diffuse SSc). In early dcSSc, an increase in skin thickening is generally associated with new or worsening internal organ involvement and increased mortality. Worsening mRSS is associated with higher mortality, and both negative renal and cardiac outcomes. Results have not been published as of October 2024. All requests for this indication are considered experimental and investigational.

Appendix

I. Table 1: Topical Corticosteroid Potency Chart

Potency Group	Corticosteroid	Vehicle type/form	Brand names	Available strength(s), percent (except as noted)
Super-high potency (Group 1)	Betamethasone dipropionate, augmented	Gel, lotion, ointment (optimized)	Diprolene	0.05
	Clobetasol propionate	Cream, gel, ointment, solution (scalp)	Temovate	0.05
		Cream, emollient base	Temovate E	0.05
		Lotion, shampoo, spray aerosol	Clobex	0.05
		Foam aerosol	Olux-E, Tovet	0.05
		Solution (scalp)	Cormax	0.05
	Fluocinonide	Cream	Vanos	0.1
	Flurandrenolide	Tape (roll)	Cordran	4 mcg/cm2
	Halobetasol propionate	Cream, lotion, ointment	Ultravate	0.05
High potency (Group 2)	Amcinonide	Ointment	Cyclocort [¶] , Amcort [¶]	0.1
	Betamethasone dipropionate	Ointment	Diprosone [¶]	0.05
		Cream, augmented formulation (AF)	Diprolene AF	0.05
	Clobetasol propionate	Cream	Impoyz	0.025
	Desoximetasone	Cream, ointment, spray	Topicort	0.25
		Gel	Topicort	0.05
	Diflorasone diacetate	Ointment	ApexiCon [¶] , Florone [¶]	0.05
		Cream, emollient	ApexiCon E	0.05
	Fluocinonide	Cream, gel, ointment, solution	Lidex [¶]	0.05
High potency (Group 3)	Halcinonide	Cream, ointment, solution	Halog	0.1
		Lotion	Bryhali	0.01
	Halobetasol propionate	Cream	Cyclocort [¶] , Amcort [¶]	0.1
		Lotion	Amcort [¶]	0.1
	Betamethasone dipropionate	Cream, hydrophilic emollient	Diprosone [¶]	0.05
	Betamethasone valerate	Ointment	Valisone [¶]	0.1
		Foam	Luxiq	0.12
	Desoximetasone	Cream	Topicort LP [¶]	0.05
	Diflorasone diacetate	Cream	Florone [¶]	0.05

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	Diflucortolone valerate (not available in United States)	Cream, oily cream, ointment	Nerisone (Canada, United Kingdom, others)	0.1
	Fluocinonide	Cream aqueous emollient	Lidex-E¶	0.05
	Fluticasone propionate	Ointment	Cutivate	0.005
	Mometasone furoate	Ointment	Elocon	0.1
	Triamcinolone acetonide	Cream, ointment	Aristocort HP¶, Kenalog¶, Triderm	0.5
Medium potency (Group 4)	Betamethasone dipropionate	Spray	Sernivo	0.05
	Clocortolone pivalate	Cream	Cloderm	0.1
	Fluocinolone acetonide	Ointment	Synalar¶	0.025
	Flurandrenolide	Ointment	Cordran	0.05
	Hydrocortisone valerate	Ointment	Westcort	0.2
	Mometasone furoate	Cream, lotion, ointment, solution	Elocon¶	0.1
	Triamcinolone acetonide	Cream	Kenalog¶, Triderm	0.1
		Ointment	Kenalog¶	0.1
		Ointment	Trianex	0.05
		Aerosol spray	Kenalog	0.2 mg per 2 second spray
		Dental paste	Oralene	0.1
Lower-mid potency (Group 5)	Betamethasone dipropionate	Lotion	Diprosone¶	0.05
	Betamethasone valerate	Cream	Beta-Val, Valisone¶	0.1
	Desonide	Ointment	DesOwen, Tridesilon¶	0.05
		Gel	Desonate	0.05
	Fluocinolone acetonide	Cream	Synalar¶	0.025
	Flurandrenolide	Cream, lotion	Cordran	0.05
	Fluticasone propionate	Cream, lotion	Cutivate	0.05
	Hydrocortisone butyrate	Cream, lotion, ointment, solution	Locoid, Locoid Lipocream	0.1
	Hydrocortisone probutate	Cream	Pandel	0.1
	Hydrocortisone valerate	Cream	Westcort¶	0.2
	Prednicarbate	Cream (emollient), ointment	Dermatop	0.1
	Triamcinolone acetonide	Lotion	Kenalog¶	0.1
		Ointment	Kenalog¶	0.025
Low potency (Group 6)	Alclometasone dipropionate	Cream, ointment	Aclovate	0.05
	Betamethasone valerate	Lotion	Beta-Val¶, Valisone¶	0.1
	Desonide	Cream	DesOwen, Tridesilon¶	0.05
		Lotion	DesOwen, LoKara	0.05
		Foam	Verdeso	0.05
	Fluocinolone acetonide	Cream, solution	Synalar¶	0.01
		Shampoo	Capex	0.01
		Oil (48% refined peanut oil)	Derma-Smoothe/FS Body, Derma-Smoothe/FS Scalp	0.01
	Triamcinolone acetonide	Cream, lotion	Kenalog¶, Aristocort¶	0.025
Least potent (Group 7)	Hydrocortisone (base, ≥2%)	Cream, ointment	Hytone, Nutracort¶	2.5
		Lotion	Hytone, Ala Scalp, Scalacort	2
		Solution	Texacort	2.5
	Hydrocortisone (base, <2%)	Ointment	Cortaid, Cortizone 10, Hytone, Nutracort	1

		Cream	Cortaid¶, Cortizone 10, Hytone, Synacort	1
		Gel	Cortizone 10	1
		Lotion	Aquanil HC, Sarnol-HC, Cortizone 10	1
		Spray	Cortaid	1
		Solution	Cortaid, Noble, Scalp Relief	1
		Cream, ointment	Cortaid	0.5
	Hydrocortisone acetate	Cream	MiCort-HC	2.5
		Lotion	Nucort	2

¶ Inactive United States brand name for specific product; brand may be available outside United States

References

1. Nemluvio (nemolizumab). Package Insert. Galderma Laboratories, L.P., Dallas, TX. December 2024.
2. Kwatra SG, Yosipovitch G, Legat FJ, et al. Phase 3 Trial of Nemolizumab in Patients with Prurigo Nodularis. N Engl J Med. 2023;389(17):1579-1589. doi:10.1056/NEJMoa2301333
3. American Academy of Dermatology 2020 Practice Approaches Guidelines to Prurigo Nodularis. Accessed July 10, 2024. <https://doi.org/10.1016/j.jaad.2020.07.025>
4. UpToDate, Inc. Topical corticosteroids: Use and adverse effects. UpToDate [database online]. Waltham, MA. Updated Feb 2024. Accessed July 11, 2024.
5. Yosipovitch, Gil; Stander, Sonja; Metz, Martin. Nemolizumab monotherapy improves itch, sleep disturbance, and skin lesions in patients with moderate to severe prurigo nodularis: Polled analyses from OLYMPIA 1 and OLYMPIA 2 phase 3 studies. Poster presented at 6th Annual revolutionizing atopic dermatitis (RAD) conference, June 8-10, 2024, Chicago, IL.

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)	Prurigo Nodularis
dupilumab (Dupixent)	Atopic Dermatitis
Lebrikizumab (Ebglyss)	
tralokinumab (Adbry)	
Systemic Janus Associated Kinase (JAK) Inhibitors in Chronic Inflammatory Disease	
ruxolitinib (Jakafi, Opzelura)	

Policy Implementation/Update:

Action and Summary of Changes	Date
Update to the criteria for AD to include in combination on initial review only, following label.	2/2025
Policy created	11/2024

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Policy Type: PA/SP

Pharmacy Coverage Policy: UMP077

Split Fill Management*

Description

Neratinib (Nerlynx) is an orally administered Epidermal Growth Factor Receptor (EGFR), Human Epidermal Growth Factor Receptor 2 and 4 (HER2, HER4) irreversible inhibitor.

Length of Authorization

- Initial:
 - i. Early stage breast cancer: 12 months
 - ii. Metastatic breast cancer: Six months
- Renewal:
 - i. Early stage breast cancer: Cannot be renewed
 - ii. Metastatic breast cancer: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
neratinib (Nerlynx)	40 mg tablets	Breast cancer, early stage, HER2-positive, following trastuzumab	180 tablets/30 days
		Breast cancer, advanced or metastatic HER2-positive	

Initial Evaluation

- I. Neratinib (Nerlynx) may be considered medically necessary when the following criteria are met:
 - A. Member is a female 18 years of age or older; **AND**
 - B. Medication is prescribed by, or in consultation with, an oncologist; **AND**
 - C. Neratinib (Nerlynx) will **not** be used in combination with another oncology therapy unless outlined below (e.g. in combination with capecitabine in metastatic disease); **AND**
 - D. The member has **not** previously progressed on, or after, treatment with another tyrosine kinase inhibitor (e.g., lapatinib [Tykerb], tucatinib [Tukysa]); **AND**
 - E. A diagnosis of one of the following:
 1. **Early stage (I-III) breast cancer; AND**
 - i. Documentation is provided showing the disease is HER2-positive AND hormone receptor (HR)-positive; **AND**
 - ii. The member has received adjuvant trastuzumab-based therapy (e.g., Herceptin, Trazimera, Kanjinti, etc.) within the past 12 months; **OR**
 2. **Advanced or metastatic breast cancer; AND**
 - i. Documentation is provided showing the disease is HER2-positive; **AND**

- ii. Member has received ≥ 2 prior anti-HER2-based regimens [e.g., trastuzumab (Herceptin), pertuzumab (Perjeta), trastuzumab emtansine (Kadcyla; TDM-1)] in the metastatic setting; **AND**
 - iii. Will be used in combination with capecitabine
- II. Neratinib (Nerlynx) is considered not medically necessary when criteria above are not met and/or when used for:
 - A. Early stage breast cancer in members that have not received trastuzumab (e.g., Herceptin, Trazimera, Kanjinti, etc.) in the past 12 months
 - B. Early stage breast cancer that is not HR-positive
 - C. Early stage breast cancer in combination with trastuzumab (e.g., Herceptin, Trazimera, Kanjinti, etc.)
- III. Neratinib (Nerlynx) is considered investigational when used for all other conditions, including but not limited to:
 - A. Triple negative breast cancer
 - B. Breast cancer that is HER-2 negative
 - C. Non-small cell lung cancer
 - D. Colorectal cancer
 - E. Head and neck cancer
 - F. Ovarian, endometrial, uterine cancer
 - G. Bladder or rectal cancer
 - H. Early stage breast cancer for greater than one year
 - I. Solid tumors, other than breast 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; **AND**
- IV. A diagnosis of **advanced or metastatic breast cancer**; **AND**
 - Will be used in combination with capecitabine; **AND**
 - Will not be used with any other oncology therapy outside of capecitabine; **AND**
 - Disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread

Supporting Evidence

- I. Neratinib (Nerlynx) was evaluated for safety and efficacy in the ExteNET trial; a randomized, double-blind, placebo-controlled trial in women who had been previously treated with trastuzumab therapy and had HER2-positive breast cancer.
- II. Subjects included had early stage (I-III) disease and had completed trastuzumab within the past two years; however, the majority of subjects had received trastuzumab within the past year (81%). Notably, results were statistically significant in those that received trastuzumab within the past year and were not for those that had received treatment 1-2 years prior. The primary outcome was invasive disease-free survival (iDFS) defined as time between date of randomization to first occurrence of invasive recurrence. Results for the iDFS at 24 months was 94.2% for neratinib (Nerlynx) compared to 91.9% for placebo (HR 0.66 [0.49-0.90], $p=0.008$). Subgroup analyses showed a statistically significant result for those with HR-positive disease but did not for HR-negative disease. Additionally, results favored neratinib (Nerlynx) in those that used therapy after trastuzumab; however, were not significant for those concurrently receiving trastuzumab.
- III. Neratinib (Nerlynx) has only been evaluated for safety and efficacy for up to one year of therapy in early stage disease; matching the prescribing information, which notes continuous dosing for one year in this setting.
- IV. Neratinib (Nerlynx) was evaluated for safety and efficacy in the advanced or metastatic population in the NALA trial; a randomized, open label, trial evaluating neratinib (Nerlynx) plus capecitabine compared to lapatinib (Tykerb). Patients included in the trial had metastatic HER2-positive breast cancer and had received 2 or more prior anti-HER2 regimens [e.g., trastuzumab (Herceptin), pertuzumab (Perjeta), trastuzumab emtansine (Kadcyla; TDM-1)] in the metastatic setting. Median progression free survival (PFS) was 5.6 months with neratinib (Nerlynx) plus capecitabine and 5.5 months with lapatinib plus capecitabine (HR, 0.76; 95% [CI], 0.63 to 0.93; $P=0.0059$). Overall survival was 21.0 months with the neratinib (Nerlynx) arm and 18.7 months with the lapatinib arm; however, the between group difference was not statistically significant (HR, 0.88; 95% CI, 0.72 to 1.07; $P=0.2086$).
- V. Patients in the NALA trial were excluded if they were previously treated with capecitabine, neratinib, lapatinib, or any other HER2 directed tyrosine kinase inhibitor. At this time, there is a lack of scientific evaluation for safety and efficacy of neratinib (Nerlynx) following progression on, or after, another tyrosine kinase inhibitor.
- VI. In the NALA trial, 59% of patients were hormone receptor positive (HR+) and 41% were hormone receptor negative (HR-). Thus, coverage of neratinib (Nerlynx) is available regardless of hormone receptor status.
- VII. ER testing should be used to determine if a patient is a candidate for endocrine therapies. Per NCCN guidelines, women with Stage IV or recurrent disease characterized by tumors that are HR-positive, HER2-positive tumors have the option of receiving HER2-directed therapy as a component of their treatment plan. Options include, treatment with a HER2-targeted therapy plus chemotherapy or endocrine therapy alone or in combination with HER2-targeted therapy. Endocrine therapy alone or in combination with HER2-targeted therapy is a less toxic approach compared with HER2-targeted therapy combined with chemotherapy. Premenopausal women treated with HER2-targeted therapy and endocrine therapy should receive ovarian suppression or ablation.

Investigational or Not Medically Necessary Uses

- I. In the early stage breast cancer pivotal trial, ExteNET, subgroup analyses showed non statistically significant results for neratinib (Nerlynx) in the following populations:
 - A. Breast cancer in members that have not received trastuzumab (e.g., Herceptin, Trazimera, Kanjinti, etc.) in the past 12 months
 - B. Breast cancer that is not HR-positive
 - C. Breast cancer in combination with trastuzumab (e.g., Herceptin, Trazimera, Kanjinti, etc.)
- II. Neratinib (Nerlynx) has not been sufficiently evaluated for safety and efficacy in the following settings:
 - A. Triple negative breast cancer
 - B. Breast cancer that is HER-2 negative
 - C. Non-small cell lung cancer
 - D. Colorectal cancer
 - E. Head and neck cancer
 - F. Ovarian, endometrial, uterine cancer
 - G. Bladder or rectal cancer
 - H. Breast cancer for greater than one year
 - I. Solid tumors, other than breast 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.*

References

1. NCCN Clinical Practice Guideline in Oncology: Breast Cancer. Version 4.2020. National Comprehensive Cancer Network. Available at https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. Updated May 8, 2020.
2. Nerlynx [Prescribing Information]. Los Angeles, CA. Puma Biotechnology, Inc. February 2020.
3. Chan PA, Delaloge S., Holmes FA., et al. Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2016;17(3): 367-377.
4. Puma Biotechnology, Inc. A study of neratinib plus capecitabine versus lapatinib plus capecitabine in patients with HER2+ metastatic breast cancer who have received two or more prior HER2 directed regimens in the metastatic setting (NALA). Available from: <http://www.clinicaltrials.gov/ct2/show/NCT01808573>. NLM identifier: NCT01808573.

Policy Implementation/Update:

Action and Summary of Changes	Date
Addition of new indication for advanced or metastatic breast cancer. Addition of split fill management.	07/2020
Criteria transitioned to policy, with updates to newest format: inclusion of specialty provider, clarification on concurrent therapies, age requirement.	10/2019
Criteria created	09/2017

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Policy Type: PA/SP

Pharmacy Coverage Policy: UMP136

Split Fill Management* (Applies to Tasigna only)

Description

Nilotinib (Tasigna; Danziten) is a Bcr-Abl kinase inhibitor that binds to, and stabilizes, the inactive conformation of the kinase domain of the Abl protein.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
nilotinib (Tasigna)	50 mg capsules	Newly diagnosed OR resistant/intolerant Ph+ CML in chronic phase	112 capsules/28 days
	150 mg capsules	Newly diagnosed Ph+ CML in chronic phase	112 capsules/28 days
	200 mg capsules	Resistant or intolerant Ph+ CML Gastrointestinal Stromal Tumors (GIST)	112 capsules/28 days
Brand nilotinib capsule	50 mg capsules	Newly diagnosed OR resistant/intolerant Ph+ CML in chronic phase	112 capsules/28 days
	150 mg capsules	Newly diagnosed Ph+ CML in chronic phase	112 capsules/28 days
	200 mg capsules	Resistant or intolerant Ph+ CML	112 capsules/28 days
nilotinib (Danziten)	71 mg tablet	Newly diagnosed Ph+ CML-CP	112 capsules/28 days
	95 mg tablet	Resistant or intolerant Ph+ CML-CP and CML-AP	112 capsules/28 days

Initial Evaluation

- I. **Nilotinib (Tasigna; Danziten)** 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 will not be used in combination with other oncologic medications (i.e., will be used as monotherapy); **AND**
 - C. A diagnosis of one of the following:
 1. **Chronic myelogenous leukemia (CML); AND**
 - i. Request is for nilotinib (Tasigna); **OR**
 - a. Documentation of clinical rationale why nilotinib (Tasigna) would not be appropriate; **AND**
 - ii. Member is newly diagnosed with Philadelphia chromosome-positive (Ph+) or BCR-ABL1 mutation positive CML in chronic phase; **OR**
 - iii. Member is diagnosed with chronic OR accelerated phase Ph+ or BCR-ABL1 mutation positive CML; **AND**

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- a. Member is 18 years of age or older; **AND**
 - b. Treatment with a tyrosine kinase inhibitor [e.g. imatinib (Gleevec)] has been ineffective, contraindicated, or not tolerated; **OR**
 - iv. Member is diagnosed with chronic phase Ph+ or BCR-ABL1 mutation positive CML; **AND**
 - a. Member is one year of age or older; **AND**
 - b. Treatment with a tyrosine kinase inhibitor [e.g. imatinib (Gleevec)] has been ineffective, contraindicated, or not tolerated; **OR**
- 2. **Gastrointestinal Stromal Tumors (GIST); AND**
 - i. Request is for nilotinib (Tasigna); **AND**
 - ii. Treatment with ALL the following have been ineffective, contraindicated, or not tolerated:
 - a. imatinib (Gleevec)
 - b. sunitinib (Sutent)
 - c. regorafenib (Stivarga)
- II. Nilotinib (Tasigna; Danziten) is considered investigational when used for all other conditions, including but not limited to:
 - A. CML without Philadelphia chromosome
 - B. CML in the blast phase

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 use of 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. Nilotinib (Tasigna; Danziten) is prescribed by, or in consultation with, an oncologist; **AND**
- IV. Medication will not be used in combination with other oncologic medications (i.e., will be used as monotherapy); **AND**
- V. Clinical documentation of response to treatment, such as stabilization of disease or decrease in tumor size or spread is provided.

Supporting Evidence

- I. Nilotinib (Tasigna; Danziten) is FDA-approved for treatment of adult and pediatric patients greater than one year of age with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase and is a NCCN Category 1.
- II. Nilotinib (Tasigna; Danziten) for the treatment Ph+ CML resistant to prior therapy is only FDA-approved for use in the pediatric population in patients with chronic phase Ph+CML.
- III. Nilotinib (Tasigna; Danziten) is FDA-approved for use in adult patients with chronic phase and accelerated phase Ph+ CML resistant to, or intolerant of, prior therapy that included imatinib.
- IV. Payment considerations for nilotinib for the treatment of Gastrointestinal Stromal tumors is reserved for members who have tried and failed imatinib (Gleevec) and sunitinib (Sutent) for the

treatment of GIST. This recommendation is reflective of NCCN guidelines. Much of the data comes from phase II studies and retrospective analyses involving a small number of patients. In a randomized phase 3 study of nilotinib as 3rd line therapy and best supportive care (with or without a TKI) in patients with GIST resistant to imatinib and sunitinib (n=248) the PFS on nilotinib (Tasigna) was not found to be superior to best supportive care (109 days vs 111 days; P=0.56). Additionally, regorafenib has FDA approval and NCCN category 1 designation for GIST in patients previously treated with imatinib and sunitinib.

- V. Nilotinib (Danziten) is a modified formulation of nilotinib that aims to improve bioavailability and reduce the need for fasting compared to the original formulation. Both formulations provide equivalent efficacy for the treatment of CML.

Investigational or Not Medically Necessary Uses

- I. Nilotinib (Tasigna; Danziten) has not been sufficiently evaluated in the following settings. Limited evidence may be available; however, safety and efficacy have not been established for:
 - A. CML without Philadelphia chromosome
 - B. CML in the blast phase

** 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. Tasigna [Prescribing Information]. East Hanover, NJ: Novartis; September 2019.
2. National Comprehensive Cancer Network (NCCN); Clinical Practice Guidelines in Oncology: Chronic Myelogenous Leukemia – v.2.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf.
3. National Comprehensive Cancer Network (NCCN); Clinical Practice Guidelines in Oncology: Soft Tissue Sarcoma – v.3.2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf.

Policy Implementation/Update:

Action and Summary of Changes	Date
Require clinical rationale for use of Danziten instead of Tasigna	03/2025
Added new formulation Danziten to the policy	12/2024
Prior authorization criteria were transitioned into policy format. Expanded renewal duration from 6 months to 12 months for all indications. Required the agent to be used as monotherapy and not in combination with other oncologic medications.	12/2019
Added new indication in pediatric patients one year of age or older with Philadelphia chromosome-positive chronic myeloid leukemia in the chronic phase (Ph+ CML-CP). Allowed for approval in the second line CML setting after being treated with a TKI (other than imatinib). For GIST off-label use, added a requirement to try/fail regorafenib as well as the existing agents (imatinib and sunitinib).	05/2018
Previous review dates	02/2012; 03/2012; 07/2012; 08/2012; 01/2013;
Policy Created	08/2010

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Policy Type: PA

Pharmacy Coverage Policy: UMP199

Description

Nilutamide (Nilandron) is an orally active first-generation nonsteroidal antiandrogen agent, which blocks effects of testosterone at the androgen receptor level, preventing androgen response.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
Nilutamide (Nilandron)*	150 mg tablet	Metastatic prostate cancer	Initial: 60 tablets/ 30 days for one month Maintenance: 30 tablets/ 30 days

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

Initial Evaluation

- I. Nilutamide (Nilandron) may be considered medically necessary when following criteria are met:
 - A. 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. A diagnosis of **metastatic prostate cancer**; **AND**
 - D. Treatment with generic nilutamide has been ineffective, contraindicated or not tolerated
- II. Nilutamide (Nilandron) 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 has absence of unacceptable toxicity from the medication; **AND**
- III. Disease response to treatment defined by stabilization of disease or decrease in tumor size or tumor spread

Supporting Evidence

- I. Nilutamide (Nilandron) is an orally active antiandrogen drug that works by blocking the effects of testosterone at the androgen receptor level thereby preventing an androgenic response. Nilandron interrupts the effect that testosterone has on the prostate and deprives it of signals typically responsible for growth and cell differentiation in the prostate.
- II. Nilutamide (Nilandron) is FDA-approved for adult members (18 years and older) as a combination agent with surgical castration for the treatment of metastatic prostate cancer (Stage D2).
- III. There are multiple treatment modalities for prostate cancer, wherein the choice of therapy depends 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. Therefore, nilutamide (Nilandron) should be prescribed by, or in consultation with, and oncologist or urologist.
- IV. Coverage of brand name nilutamide (Nilandron) requires failure, intolerance or contraindication to generic nilutamide. Nilutamide is the AB-rated generic to nilutamide (Nilandron), and is deemed to be bioequivalent to the brand formulation; however, is a more cost-effective option.

References

1. Nilandron (nilutamide) [prescribing information]. St. Michael, Barbados: Concordia Pharmaceuticals; received May 2017.
2. Orange Book: approved drug products with therapeutic equivalence evaluations. U.S. Food & Drug Administration. Accessed October 2020. Available at: https://www.accessdata.fda.gov/scripts/cder/ob/search_product.cfm

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	10/2020

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP138

Split Fill Management*

Description

Nintedanib (Ofev) is an orally administered tyrosine kinase inhibitor.

Pirfenidone (Esbriet) is an orally administered pyridine that is thought to exert antifibrotic properties by decreasing fibroblast proliferation and the production of fibrosis associated proteins and cytokines.

Length of Authorization

- Initial:
 - Esbriet: 12 months
 - Ofev: Three months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
nintedanib (Ofev)	Idiopathic pulmonary fibrosis (IPF); Systemic sclerosis-associated interstitial lung disease (SSc-ILD); Chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype	100 mg capsules	60 capsules/30 days
		150 mg capsules	
pirfenidone (generic Esbriet)	Idiopathic Pulmonary Fibrosis (IPF)	267 mg capsules or tablets	270 capsules or tablets/30 days
		534 mg tablets	120 tablets/30 days
		801 mg tablets	90 tablets/30 days
pirfenidone (Esbriet)	Idiopathic Pulmonary Fibrosis (IPF)	267 mg capsules or tablets	270 capsules or tablets/30 days
		801 mg tablets	90 tablets/30 days

Initial Evaluation

- I. **Nintedanib (Ofev) and prifenidone (Esbriet)** 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 pulmonologist; **AND**

- C. Nintedanib (Ofev) and pirfenidone (Esbriet) will not be used in combination with each other; **AND**
 - D. Provider attests the member is currently abstaining from any form of smoking; **AND**
 - E. Documentation of baseline assessment [forced vital capacity (%FVC) **OR** carbon monoxide diffusing capacity (DLCO) **OR** six-minute walking distance (6MWD)]; **AND**
 - F. A diagnosis of one of the following:
 - 1. **Idiopathic pulmonary fibrosis (IPF); AND**
 - i. Member has a usual interstitial pneumonia pattern (UIP) confirmed by a high resolution computed tomographic (HRCT) scan or surgical lung biopsy; **AND**
 - ii. The request is for generic pirfenidone tablets; **OR**
 - a. The request is for generic pirfenidone capsules, and treatment with generic pirfenidone tablets has been ineffective, not tolerated, or contraindicated; **OR**
 - b. The request is for brand Esbriet; **AND**
 - i. Treatment with generic pirfenidone tablets has been ineffective, not tolerated, or contraindicated; **AND**
 - ii. Treatment with generic pirfenidone capsules has been ineffective, not tolerated, or contraindicated; **OR**
 - iii. If the request is Nintedanib (Ofev), treatment with generic pirfenidone tablets has been ineffective, not tolerated, or contraindicated; **OR**
 - 2. **Systemic sclerosis-associated interstitial lung disease (SSc-ILD); AND**
 - i. Request is for nintedanib (Ofev); **AND**
 - ii. The diagnosis confirmed by a high resolution computed tomographic (HRCT) scan; **OR**
 - 3. **Chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype; AND**
 - i. Request is for nintedanib (Ofev); **AND**
 - ii. Member has fibrotic features in lungs confirmed by a high resolution computed tomographic (HRCT) scan; **AND**
 - iii. Member has clinical signs of progression (eg. decline in %FVC with worsening respiratory symptoms **or** increasing extent of fibrotic changes on chest imaging)
- II. Nintedanib (Ofev) and pirfenidone (Esbriet) are considered investigational when used for all other conditions, including but not limited to:
- A. Bronchiolitis Obliterans Syndrome (BOS)
 - B. Lymphangioleiomyomatosis (LAM)
 - C. Non-Small Cell Lung Cancer (NSCLC)
 - D. Malignant Pleural Mesothelioma (MPM)
 - E. Esophagogastric Cancer
 - F. Thyroid Cancer
 - G. Breast Cancer
 - H. Ovarian Cancer

- I. Pancreatic Cancer
- J. Used in combination with other medications within this policy
- K. Multiple Sclerosis
- L. Chronic Lung Allograft Dysfunction
- M. Radiation-induced Lung Injury
- N. Diabetic nephropathy
- O. Glomerulosclerosis
- P. Cardiac Failure

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through the health plan; **AND**
- II. The member is not continuing therapy based off established therapy through samples, manufacturer coupons, or otherwise. Initial policy criteria must be met for the member to qualify for continuation through this health plan; **AND**
- III. Provider attests that member has exhibited improvement or stability of disease symptoms (e.g., increase in forced vital capacity (%FVC), carbon monoxide diffusing capacity (DLCO), or six-minute walking distance (6MWD) from baseline); **AND**
- IV. Nintedanib (Ofev) and pirfenidone (Esbriet) will not be used in combination with each other; **AND**
- V. Provider attests that member is currently abstaining from any form of smoking; **AND**
- VI. A diagnosis of one of the following:
 - a. **Idiopathic pulmonary fibrosis (IPF); AND**
 - 1. The request is for nintedanib (Ofev); **OR**
 - 2. The request is for generic pirfenidone tablets; **OR**
 - a. The request is for generic pirfenidone capsules, and treatment with generic pirfenidone tablets has been ineffective, not tolerated, or contraindicated; **OR**
 - b. The request is for brand Esbriet; **AND**
 - i. Treatment with generic pirfenidone tablets has been ineffective, not tolerated, or contraindicated; **AND**
 - ii. Treatment with generic pirfenidone capsules has been ineffective, not tolerated, or contraindicated; **OR**
 - b. **Systemic sclerosis-associated interstitial lung disease (SSc-ILD); AND**
 - i. Request is for nintedanib (Ofev); **OR**
 - c. **Chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype; AND**
 - i. Request is for nintedanib (Ofev)

Supporting Evidence

- I. Nintedanib (Ofev) inhibits multiple receptor tyrosine kinases (RTKs) and non-receptor tyrosine kinases (nRTKs). It binds competitively to the adenosine triphosphate (ATP) binding pocket of these kinases and blocks the intracellular signaling 13 cascades.

- II. Idiopathic pulmonary fibrosis (IPF) is an idiopathic chronic fibrosing interstitial pneumonia with a histopathologic or radiographic pattern of usual interstitial pneumonia (UIP).
- III. High resolution computed tomography (HRCT) should be obtained in all patients suspected of having IPF. When the results of the HRCT cannot allow the clinician to make a confident diagnosis of IPF, surgical lung biopsy may be warranted. However, the decision requires assessment of the benefits of having a definitive diagnosis relative to the risks of the surgical procedure.
- IV. For the treatment of IPF, nintedanib (Ofev) was studied in 1,066 patients with IPF in two Phase 3 trials (INPULSIS-1 and INPULSIS-2). These were randomized, double-blind, placebo-controlled studies comparing treatment with nintedanib (Ofev) 150 mg twice daily to placebo for 52 weeks.

- The primary outcome: The adjusted annual rate of change in FVC (in mL):
 - i. INPULSIS-1: -114.7 mL per year in the nintedanib (Ofev) group and -239.9 mL per year in the placebo group over week 52 (absolute difference of 125.2 mL, 95% CI: 77.7, 172.8; $p<0.001$)
 - ii. INPULSIS-2: -113.6 mL per year in the nintedanib (Ofev) group and -207.3 mL per year in the placebo group over week 52 (absolute difference of 93.7 mL, 95% CI: 44.8, 142.7; $p<0.001$)
- The secondary lung function outcomes:

End Points	INPULSIS-1			INPULSIS-2		
	Nintedanib (N=307)	Placebo (N=204)	95% CI; <i>P</i> value	Nintedanib (N=327)	Placebo (N=217)	95% CI; <i>P</i> value
Adjusted absolute mean change from baseline in FVC (mL)	-95.1	-205.0	109.9 (71.3, 148.6; $P<0.001$)	-95.3	-205.0	109.8 (70.9, 148.6; $P<0.001$)
Adjusted absolute mean change from baseline in FVC (% predicted)	-2.8%	-6.0%	3.2% (2.1, 4.3; $P<0.001$)	-3.1%	-6.2%	3.1% (1.9, 4.3; $P<0.001$)
FVC response at week 52 (%): FVC decline $\leq$ 5%	52.8%	38.2%	1.85% (1.28, 2.66; $p=0.001$)	53.2%	39.3%	1.79% (1.23, 2.55; $p=0.001$)
FVC response at week 52 (%): FVC decline $\leq$ 10%	70.6%	56.9%	1.91% (1.32, 2.79; $P<0.001$)	69.6%	63.9%	1.29% (0.89, 1.86; $p=0.18$)

- V. The presence of SSc-ILD is defined by the identification of fibrotic features on HRCT scan. Surgical lung biopsy is seldom performed in SSc patients, unless the HRCT pattern is atypical, there is suspicion of a different diagnosis, or there is a complication such as cancer.
- VI. Pulmonary function tests (PFT) in patients with SSc-ILD demonstrate a restrictive pattern, with FVC and diffusion capacity of the lung for carbon monoxide (DLCO). DLCO is a measure of the conductance of gas transfer from inspired gas to the red blood cells. A low DLCO combined with reduced lung volumes suggests interstitial lung disease (ILD).
- VII. For systemic sclerosis-associated interstitial lung disease (SSc-ILD), nintedanib (Ofev) was studied in a Phase 3, randomized, double-blind, placebo-controlled trial (N=576) (SENSCIS trial). Patients received either nintedanib (Ofev) 150 mg twice daily (N=228) or placebo (N=288) for at least 52 weeks.
 - The primary outcome: The adjusted annual rate of change in FVC (in mL): -52.4 mL per year in the nintedanib (Ofev) group and -93.3 mL per year in the placebo group over week 52 (absolute difference of 40.9 mL, 95% CI: 2.9, 79.0; $p=0.04$).
- VIII. Safety and efficacy of nintedanib (Ofev) have not been established in pediatric patients.

- IX. The safety and efficacy of pirfenidone (Esbriet) was studied in three phase 3, randomized, double-blind, placebo-controlled, multicenter trials in patients (40 to 80 years of age) with idiopathic pulmonary fibrosis (IPF) and a %FVC of at least 50%.
 - A. Study One: 52-week trial comparing pirfenidone (Esbriet) 2403 mg/day (n=278) versus placebo (n=277). The primary efficacy outcome for the change in %FVC at week 52 demonstrated a statistically significant treatment effect with pirfenidone (Esbriet) when compared to placebo.
 - B. Study Two: 72-week trial comparing pirfenidone (Esbriet) 2403 mg/day (n=174) or pirfenidone (Esbriet) 1197 mg/day (n=87) to placebo (n=174). The primary efficacy outcome for the change in %FVC at week 72 demonstrated a statistically significant treatment effect with pirfenidone (Esbriet) when compared to placebo.
 - C. Study Three: 72-week trial comparing pirfenidone (Esbriet) 2403 mg/day (n=171) to placebo (n=173). In this study, there was no statistically significant difference at week 72 for the change in %FVC from baseline when compared to placebo.
- X. The exact etiology of IPF is not known, but the associated risk factors include cigarette smoking, viral infection, environmental pollutants, chronic aspiration, genetic predisposition, and drugs.
- XI. According to the American Thoracic Society guidelines, the diagnosis of IPF requires:
 - A. Exclusion of other known causes of interstitial lung disease (ILD) (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity).
 - B. The presence of a usual interstitial pneumonia (UIP) pattern on high-resolution computed tomography (HRCT) in patients not subjected to surgical lung biopsy.
 - C. Specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy.
- XII. The clinical efficacy of nitendanib (Ofev) has been studied in patients with chronic fibrosing ILDs with a progressive phenotype in a randomized, double-blind, placebo-controlled phase 3 trial (Study 5). A total of 663 patients were randomized in a 1:1 ratio to receive either nitendanib (Ofev) 150 mg twice daily or matching placebo for at least 52 weeks. Randomization was stratified based on high resolution computed tomography (HRCT) fibrotic pattern.
 - A. The primary endpoint was the annual rate of decline in FVC (in mL) over 52 weeks. There was a statistically significant reduction by 107 mL in patients receiving OFEV compared to patients receiving placebo.
- XIII. High-resolution computed tomography (HRCT) of the chest is mandatory in order to assess if ILD is present and, if so, to begin the differential diagnosis.
- XIV. Progression of fibrosing ILDs is reflected in an increase in fibrosis evident on a computed tomography scan, a decline in FVC and gas exchange (DLCO), worsening of symptoms and exercise capacity (6MWD), and deterioration in health-related quality of life.
 - A. There is no standardized definition of PF-ILD that clinicians and researchers have agreed upon. Several criteria have been used to define progression in patients with IPF, with most of these based on an absolute or relative decline in FVC and diffusing capacity of the lung for DLCO of greater than or equal to 5–10% or greater than or equal to 10–15%, a decline in 6MWD > 50 m, or worsening dyspnea and quality of life scores. FVC is a reliable, valid, and responsive measure of clinical status in patients, and a decline of 2-6%, although small, represents a clinically important difference. FVC is used as a surrogate marker of disease severity and progression. DLCO is considered a

standard predictor of survival. The distance walked in the 6MWT is used in a variety of pulmonary diseases and is predictive of mortality.

Investigational or Not Medically Necessary Uses

- I. There is currently no evidence to suggest safety and/or efficacy with nitendanib (Ofev) or pirfenidone (Esbriet), when used for the treatment of bronchiolitis obliterans syndrome (BOS), lymphangioleiomyomatosis (LAM), non-small cell lung cancer (NSCLC), malignant pleural mesothelioma (MPM), esophagogastric cancer, thyroid cancer, breast cancer, ovarian cancer, or pancreatic cancer. Further there is no evidence to support the use of nitendanib (Ofev) in combination with pirfenidone (Esbriet).

** 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. Ofev [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2019.
2. Raghu G, Remy-jardin M, Myers JL, et al. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. *Am J Respir Crit Care Med*. 2018;198(5):e44-e68. doi: 10.1164/rccm.201807-1255ST.
3. Richeldi L, Du bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med*. 2014;370(22):2071-82. doi: 10.1056/NEJMoa1402584.
4. Distler O, Highland KB, Gahlemann M, et al. Nintedanib for Systemic Sclerosis-Associated Interstitial Lung Disease. *N Engl J Med*. 2019;380(26):2518-2528. doi: 10.1056/NEJMoa1903076.
5. Cottin V, Brown KK. Interstitial lung disease associated with systemic sclerosis (SSc-ILD). *Respir Res*. 2019;20(1):13. doi: 10.1186/s12931-019-0980-7.
6. Esbriet [Prescribing Information]. South San Francisco, CA: Genentech, Inc. July 2019.
7. Wells AU, Flaherty KR, Brown KK, et al. Nintedanib in patients with progressive fibrosing interstitial lung diseases-subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial. *Lancet Respir Med*. 2020 Mar 5. pii: S2213-2600(20)30036-9. doi: 10.1016/S2213-2600(20)30036-9.
8. Vincent Cottin, Lutz Wollin, Aryeh Fischer, et al. Fibrosing interstitial lung diseases: knowns and unknowns. *European Respiratory Review* 2019 28: 180100; DOI: 10.1183/16000617.0100-2018
9. du Bois RM, Weycker D, Albera C, et al. Forced vital capacity in patients with idiopathic pulmonary fibrosis: test properties and minimal clinically important difference. *Am J Respir Crit Care Med* 2011; 184: 1382–1389.
10. Loveman E, Copley VR, Colquitt J, et al. The clinical effectiveness and cost-effectiveness of treatments for idiopathic pulmonary fibrosis: a systematic review and economic evaluation. NIHR Journals Library; 2015 Mar.
11. Wong, A. W., Ryerson, C. J., & Guler, S. A. (2020). Progression of fibrosing interstitial lung disease. *Respiratory research*, 21(1), 32. <https://doi.org/10.1186/s12931-020-1296-3>

Policy Implementation/Update:

Action and Summary of Changes	Date
Added step for branded Esbriet through both generic tablets and capsules prior to brand use; added step through generic tablets prior to use of generic capsules	01/2023
Added generic pirfenidone 534mg tablets to QL table	08/2022
Added new generic pirfenidone, requiring trial of generic pirfenidone prior to brand Esbriet	06/2022
- Added nintedanib (Ofev) to the Moda Split Fill program - Added criteria for nintedanib (Ofev) new indication Chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype [request is for nintedanib (Ofev) and member has greater than 10% fibrotic features confirmed by a high resolution computed tomographic (HRCT) scan and clinical signs of progression (eg. decline in %FVC with worsening of respiratory symptoms, or increasing extent of fibrotic changes on chest imaging)]. - Added criteria for baseline assessment [eg. forced vital capacity (%FVC) or carbon monoxide diffusing capacity (DLCO) or six minute walking distance (6MWD)]	06/2020
Criteria updated to new policy format. Specific changes include: Updated idiopathic pulmonary fibrosis (IPF) initial evaluation. Combined policies with pirfenidone (Esbriet) for the indication of idiopathic pulmonary fibrosis (IPF). Added new indication of systemic sclerosis-associated interstitial lung disease (SSc-ILD), SSc-ILD initial evaluation, investigational use, and renewal evaluation. Added new supporting evidences and references.	12/2019
Policy created	10/2014

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP139

Split Fill Management*

Description

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

Niraparib-abiraterone acetate (Akeega) is a combination therapy containing abiraterone, an androgen biosynthesis inhibitor, indicated for prostate cancer.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
niraparib (Zejula)	<u>Maintenance for:</u> recurrent or advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer	100 mg capsules*	30 capsules/30 days
		100 mg tablet	30 tablets/30 days
		200 mg tablet	30 tablets/30 days
		300 mg tablet	30 tablets/30 days
niraparib-abiraterone acetate (Akeega)	Metastatic prostate cancer, Castration-resistant, deleterious or suspected deleterious BRCA-mutated	50 mg/500 mg	60 tablets/30 days
		100 mg/500 mg	60 tablets/30 days

* Capsule formulation is being withdrawn from the market by end of year 2023

Initial Evaluation

- I. **Niraparib (Zejula), niraparib-abiraterone acetate (Akeega)** 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. Medication will not be used in combination with any other oncolytic medication; **AND**
 - D. Member has not progressed on prior PARP inhibitor therapy (e.g. olaparib [Lynparza], rucaparib [Rubraca], talazoparib [Talzenna]) therapy; **AND**
 - E. The request is for niraparib (Zejula); **AND**
 1. A diagnosis of one of the following:
 - i. **Advanced (stage III or IV) ovarian, fallopian tube, or primary peritoneal cancer; AND**
 - a. Member has completed at least **one** prior platinum-based chemotherapy regimen (e.g. cisplatin, oxaliplatin, carboplatin); **AND**

- b. The member has **not** received bevacizumab (Avastin) in prior treatment; **AND**
 - c. Niraparib (Zejula) will **not** be used in combination with bevacizumab (Avastin); **OR**
 - ii. **Recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer;**
AND
 - a. Member has experienced disease progression on or after **at least two or more** prior platinum-based chemotherapy regimens (e.g., cisplatin, carboplatin, oxaliplatin); **AND**
 - b. Member had complete or partial response to prior platinum-based chemotherapy (i.e., platinum-sensitive) (e.g. cisplatin, oxaliplatin, carboplatin); **AND**
 - c. Provider attests that member's epithelial ovarian, fallopian tube, or primary peritoneal cancer has not progressed since the most recent platinum-based chemotherapy regimen (e.g. cisplatin, oxaliplatin, carboplatin); **OR**
 - F. The request is for niraparib-abiraterone (Akeega); **AND**
 - 1. A diagnosis of **metastatic, castration-resistant prostate cancer (mCRPC)**; **AND**
 - 2. Documentation of deleterious (pathogenic) or suspected deleterious (likely pathogenic) BRCA-mutation; **AND**
 - 3. Evidence of disease progression despite therapy with a gonadotropin-releasing hormone analog (GnRH) or bilateral orchiectomy; **AND**
 - i. The member has **not** had disease progression on a second-generation antiandrogen agent (e.g. abiraterone, enzalutamide (Xtandi), apalutamide (Erleada), darolutamide (Nubeqa)); **AND**
 - 4. Niraparib-abiraterone acetate (Akeega) will be used in combination with prednisone or prednisolone; **AND**
 - 5. Documentation of clinical rationale why combination therapy, abiraterone and olaparib (Lynparza), would not be an effective regimen (use of generic abiraterone 250 mg tablets required)
- II. Niraparib (Zejula) and niraparib-abiraterone acetate (Akeega) are 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. Lung 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
 - I. High risk localized or locally advanced prostate cancer
 - J. Metastatic castration resistant prostate cancer with SPOP gene 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. Provider attestation or clinical documentation of response to treatment (e.g., stabilization of disease, decrease in tumor size or tumor spread, lack of disease progression); **AND**
 - A. **Ovarian, fallopian tube, or primary peritoneal cancer; AND**
 1. Medication will not be used in combination with any other oncolytic medication;
OR
 - B. **Metastatic, castration-resistant, prostate cancer; AND**
 1. Niraparib-abiraterone (Akeega) will not be used in combination with other anti-cancer agents (outside of gonadotropin-releasing hormone agonist [e.g., leuprolide] or endocrine therapy [e.g., anastrozole, tamoxifen, fulvestrant] or bevacizumab or abiraterone); **AND**
 2. Niraparib-abiraterone acetate (Akeega) will be used in combination with prednisone or prednisolone

Supporting Evidence

Ovarian, fallopian tube, or primary peritoneal cancer

- I. The safety and efficacy of niraparib (Zejula) in the setting of maintenance therapy for recurrent ovarian cancer was studied in a double-blind, placebo-controlled trial in adult patients with platinum-sensitive recurrent epithelial, ovarian fallopian tube, or primary peritoneal cancer. The patients were randomized 2:1 niraparib (Zejula) 300 mg orally daily or matched placebo within eight weeks of the last platinum-based chemotherapy regimen. The trial demonstrated a statistically significant improvement in progression free survival (PFS) for patients randomized to niraparib (Zejula) as compared with placebo in the gBRCAmut cohort and the non-gBRCAmut cohort.
 - A. gBRCAmut Cohort: PFS in the niraparib (Zejula) arm was 21 and 5.5 in the placebo arm with a HR of 0.26 and 95% CI (0.17, 0.41).
 - B. Non-gBRCAmut Cohort: PFS in the niraparib (Zejula) arm was 9.3 and 3.9 in the placebo arm with a HR of 0.45 and 95% CI (0.34, 0.61).
- II. Therapy in the maintenance setting was initiated within eight weeks after completion of the last dose of platinum-based chemotherapy. Therefore, the inclusion of this as criteria (see above) is that treatment is started within a reasonable timeframe consistent with a maintenance treatment plan (i.e. as close to eight weeks as possible) while still recognizing that scheduling or other factors may impact the ability of a patient to start exactly within these first eight weeks.
- III. Efficacy and safety of niraparib (Zejula) in the first-line maintenance treatment was assessed in a phase three, double-blind, randomized (PRIMA) clinical trial in patients with newly diagnosed advanced (stage III or IV) ovarian cancer. Seven hundred and thirty-three patients, who were in complete or partial response to first-line platinum-based chemotherapy, were randomized 2:1 to niraparib (Zejula) or matched placebo. Patients with and without homologous recombination

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deficiency (HRD, e.g. gBRCAm) were included. At the end of treatment period, niraparib (Zejula) treatment arm showed a statistically significant improvement in median progression free survival (PFS) as compared to placebo arm.

- A. Homologous recombination deficiency (HRD; e.g. gBRCAm) cohort: median PFS was 21.9 months in niraparib (Zejula) arm and 10.4 months in placebo arm (hazard ratio 0.43; 95% CI, 0.31 to 0.59; $P < 0.001$)
- B. Overall population (without HRD; gBRCAm) cohort: median PFS was 13.8 months in niraparib (Zejula) arm and 8.2 months in placebo arm (HR 0.62; 95% CI, 0.5 to 0.76; $p < 0.001$).

None of the treated patients had a history of taking bevacizumab (Avastin). Therefore, efficacy and safety of niraparib (Zejula) after first-line therapy with bevacizumab (Avastin), or in combination with, bevacizumab (Avastin) is not supported.

- IV. During PRIMA trial, serious adverse events occurred in 98.8% (N=478) patients in the treatment arm with 70.5% being grade ≥ 3 . These numbers were 91.8% (N=224) and 46%, respectively in the placebo arm. Serious adverse events led to 79.5% dose interruption rates, 70.9% dose reduction rates, and 12% treatment discontinuation in the treatment group vs. 18%, 8.2%, and 2.5%, respectively, in the placebo group.
- V. 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.

Prostate cancer

- I. Niraparib-abiraterone acetate (Akeega) is FDA approved for the treatment of metastatic castration resistant prostate cancer (mCRPC) with *BRCA1/2* mutation.
- II. The safety and efficacy of Niraparib/abiraterone acetate (Akeega) is demonstrated in the MAGNITUDE trial, which is a randomized, double blind, placebo-controlled, phase 3 trial. A total of 423 adult patients were randomized 1:1 to either receive abiraterone/prednisone in combination with niraparib or placebo. 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 niraparib-abiraterone resulted in a 45% lower risk of radiographic progression or death compared to the placebo/abiraterone arm (HR 0.55 95% CI 0.39-0.78, $P = 0.0007$). An overall survival benefit was also seen in the *BRCA* subgroup in a prespecified IPCW analysis (HR 0.54, 95% CI 0.33-0.90, $P = 0.0181$). The most common adverse effects in the treatment group were anemia (50%), hypertension (33%), and constipation (33%). Treatment-emergent adverse events leading to dose interruption, dose reduction, or discontinuation of niraparib occurred in 49.7%, 20.3%, and 15.1% of patients in the active arm respectively. Niraparib/abiraterone for *BRCA* mutation is listed as a Category 1 recommendation per NCCN guidelines.
- III. One of the key inclusion criteria in MAGNITUDE was bilateral orchiectomy or ongoing androgen deprivation therapy (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 Akeega 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 olaparib (Lynparza) versus placebo in combination with abiraterone targeted a similar patient population as MAGNITUDE, 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 November 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.

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 niraparib (Zejula) in the following settings listed below:
- A. Used in combination with other chemotherapy or targeted therapy regimen.
 - B. Breast Cancer
 - C. Prostate Cancer
 - D. Lung Cancer
 - E. Advance Solid Tumors
 - F. Melanoma
 - G. Pancreatic cancer
 - H. Gastroesophageal cancer
 - I. Treatment of advanced ovarian cancer after 3 or more lines of therapy
 - i. Niraparib (Zejula) was studied in the QUADRA trial, evaluating niraparib (Zejula) for the treatment of advanced ovarian cancer after three or more chemotherapies. This was a single arm trial with investigator assessment of objective response rate (ORR) as the efficacy outcome measure. Given the setting of the QUADRA trial (single arm, uncontrolled nature), no comparative overall survival information can be obtained from the study, and it is difficult to assess any potential effect of niraparib (Zejula) on time to event endpoints.
 - ii. In September 2022, the manufacturer of niraparib (Zejula) 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. A potential detrimental effect on overall survival was observed with two different PARP inhibitors in two independent randomized, active-controlled clinical trials conducted in a BRCA mutant 3L+ advanced ovarian cancer population.

** 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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References

1. Zejula [Prescribing Information]. Research Triangle Park, NC: GlaxoSmithKline LLC. September 2022.
2. AKEEGA [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. August 2023.
3. González-Martín A, Pothuri B, Vergote I, et al. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. *N Engl J Med*. 2019;381(25):2391-2402
4. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines). Ovarian Cancer Including: Epithelial Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer & Less Common Histopathologies. Version 1.2020 [Updated March 11, 2020 Available from: https://www.nccn.org/professionals/physician_gls/pdf/ovarian_blocks.pdf
5. ASCO guidelines for gynecological cancer: PARP inhibitors in the management of ovarian cancer, *J. Clin. Oncol.*; 2020, e-pub 8/2020; DOI: 10.1200/JCO.20.01924
6. Chi KN, Rathkopf D, Smith MR, et al. Niraparib and Abiraterone Acetate for Metastatic Castration-Resistant Prostate Cancer. *J Clin Oncol*. 2023;41(18):3339-3351. doi:10.1200/JCO.22.01649
7. Chi KN, Sandhu S, Smith MR, et al. Niraparib plus abiraterone acetate with prednisone in patients with metastatic castration-resistant prostate cancer and homologous recombination repair gene alterations: second interim analysis of the randomized phase III MAGNITUDE trial. *Ann Oncol*. 2023;34(9):772-782. doi:10.1016/j.annonc.2023.06.009
8. National Comprehensive Cancer Network. Prostate Cancer (Version 4.2023) NCCN. September 7, 2023. Accessed October 31, 2023. [prostate.pdf \(nccn.org\)](https://www.nccn.org/prostate.pdf)

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
Olaparib (Lynparza) Policy	Breast cancer, metastatic, HER2-negative, germline BRCA-mutated (gBRCAm)
	Prostate cancer, metastatic castration-resistant (mCRPC)
Talazoparib (Talzenna) Policy	Breast cancer, locally advanced or metastatic, BRCA-mutated
	Prostate cancer, metastatic castration-resistant, homologous recombination repair (HRR) gene-mutated
Second Generation Anti-Androgen Agents	Prostate cancer

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated renewal to allow provider attestation of response to treatment (e.g., stabilization of disease, decrease in tumor size or tumor spread, lack of disease progression).	02/2024
Updated Zejula policy to include Akeega based on expanded indication in metastatic castration resistant prostate cancer (mCRPC). Updated QL table, general formatting, verbiage to align with current policies, and supporting evidence.	12/2023
Add 100, 200, and 300 mg tablets to the QL table with a 30/30 QL; reducing the QL from 90/30 due to the manufacturer's website promoting conversion to the once daily tablet (regardless of dose), rather than taking 1 to 3 capsules daily.	08/2023
Removal of ovarian cancer indication in the late line (3+) treatment setting following voluntarily withdrawal of the indication by the manufacturer.	09/2022
Addition of new indication and supporting evidence for first-line maintenance therapy in women with advanced ovarian cancer; Updated policy format to categorize recommendation for niraparib (Zejula) based treatment OR maintenance therapy; added split fill management	09/2020
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) due to the newly approved indication for late-line treatment in women with recurrent ovarian cancer, included	11/2019

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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.	
Criteria created	08/2017

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP296

Split Fill Management*

Description

Nirogacestat (Ogsiveo) is a gamma secretase inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
nirogacestat (Ogsiveo)	Desmoid Tumors	50 mg tablets	168 tablets /28 days

Initial Evaluation

- I. **Nirogacestat (Ogsiveo)** 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. Medication is not used in combination with any other oncology therapy; **AND**
 - D. A diagnosis of **desmoid tumors** confirmed by:
 1. An image-guided (CT or ultrasound) core needle or surgical biopsy of the tumor site; **AND**
 2. Confirmation of diagnosis by a soft tissue pathologist; **AND**
 3. Provider attestation that other germline mutation syndromes (i.e., familial adenomatous polyposis [FAP], Gardner syndrome) and/or myofibroblastic diseases (e.g., sarcoma, gastrointestinal stromal tumor, nodular fasciitis, leiomyoma) have been ruled out; **AND**
 - E. Documentation of tumor progression within the last 12 months; **AND**
 1. Documentation of significant symptoms (e.g., severe pain); **OR**
 2. Documentation of potential for morbidity (e.g., impairing, or threatening function, physical deformity).
- II. Nirogacestat (Ogsiveo) is considered investigational when used for all other conditions, including but not limited to:
 - A. Treatment of multiple myeloma
 - B. Treatment of ovarian cancer
 - C. Treatment in pediatrics and adolescents under the age of 18 years of age
 - D. Use of nirogacestat (Ogsiveo) in combination with other oncology therapy

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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 (e.g., tumor shrinkage, decreased morbidity, evidence of quality of life, symptoms, and/or functionality improvements)

Supporting Evidence

- I. Desmoid tumors (DT), are rare, noncancerous growths, that are unable to metastasize and occur as a result of mutations in fibroblasts of connective tissue. DT can arise anywhere in the body, but most commonly appear in the abdominal/intra-abdominal area. The clinical course is variable, often with an initial growth phase followed by long periods of arrest and regression. Symptoms commonly include pain, fatigue, deformity, and functional impairment. Although non-malignant, DT can progress in size if left untreated and increase the risk of invasion into local organs.
- II. The safety profile of nirogacestat (Ogsiveo) was reviewed in one Phase 3, international, double-blind, randomized, placebo controlled (DeFi) trial. Nirogacestat (Ogsiveo) was found to have a less favorable safety profile and resulted in significantly more side effects that led to dose reductions and permanent discontinuations compared to placebo. The nirogacestat (Ogsiveo) arm had a 42% dose reduction and 20% permanent discontinuation rate (versus 0% and 1% in the placebo arm, respectively) due to intolerable adverse events (AE). Split fill management is therefore recommended to reduce waste of unused medication due to a high risk of AE incidence, dose reduction, or permanent discontinuation with nirogacestat (Ogsiveo).
- III. Safety and efficacy for an increased dosing frequency above the FDA-approved dose of 150mg twice daily has not been studied nor well-established.
- IV. Safety and efficacy of nirogacestat (Ogsiveo) use in patients under the age of 18 has not been well-established. A Phase 2, interventional study to evaluate the efficacy and safety of nirogacestat (Ogsiveo) in pediatric patients 12 months to 18 years of age is expected to be completed by December of 2024. However, there is currently a lack of sufficient evidence or additional scientific literature to support the use of nirogacestat (Ogsiveo) in members <18 years of age.
- V. Due to rarity of disease and association with other germline mutation syndromes (i.e., familial adenomatous polyposis [FAP], Gardner syndrome), it is essential to rule out potential for differential diagnosis without association to desmoid tumors (e.g., Gardner syndrome). DT also shares similarities with other myofibroblastic diseases (e.g., sarcoma, gastrointestinal stromal tumor, nodular fasciitis, leiomyoma) with 30% to 40% of DT cases reported to be misdiagnosed following histologic analysis.
- VI. The use of nirogacestat (Ogsiveo) has not been studied in combination with other chemotherapy agents (e.g., methotrexate and vinorelbine) or tyrosine kinase inhibitors (TKI's) such as sorafenib. Due to the lack of safety and efficacy data with a combination regimen, use of nirogacestat (Ogsiveo) is not recommend with any other oncology therapy.

- VII. A definitive diagnosis of DT requires histopathologic analysis of a biopsy sample of the tumor which is examined for presence of desmoid cells. Both DTWG (2020) and NCCN soft tissue sarcoma (2023) guidelines recommend a histological diagnosis of DT via an image-guided (CT or ultrasound) core needle or surgical biopsy of the tumor site. Due to rarity of disease and association with other germline mutation syndromes (i.e., familial adenomatous polyposis [FAP], Gardner syndrome), it is essential to rule out potential for differential diagnosis without association to desmoid tumors (e.g., Gardner syndrome). Desmoid Tumors also shares similarities with other myofibroblastic diseases (e.g., sarcoma, gastrointestinal stromal tumor, nodular fasciitis, leiomyoma) with 30% to 40% of DT cases reported to be misdiagnosed following histologic analysis. NCCN guidelines recommend evaluation and treatment by a multidisciplinary team with expertise and experience in desmoid tumors; however, DTWG guidelines require confirmation of diagnosis by a soft tissue pathologist.
- VIII. Both DTWG (2020) and NCCN (V 2.2023) guidelines recommend active surveillance/observation alone until the tumor has shown progression and is accompanied by significant symptom burden, at which point, active treatment is pursued. NCCN guidelines also recommend active treatment if progression of DT is accompanied by potential for morbidity. The FDA-approved indication of nirogacestat (Ogsiveo) is specific to adult patients with progressing desmoid tumors. This indication is supported by the DeFi clinical trial which included patients with histologically confirmed diagnosis of progressing desmoid tumors within 12 months before screening. There is insufficient evidence to support the use of nirogacestat (Ogsiveo) in patients with nonprogressive DT at this time. Although guidelines also recommend earlier active treatment in the case of nonprogressive DT in anatomical locations where progression of the tumor would be morbid, there's insufficient evidence to support nirogacestat (Ogsiveo) as the treatment of choice in this scenario.
- IX. In the Phase 3, international, double-blind randomized, placebo controlled (DeFi) trial, eligible patients were required to have progressing DT and either had not received previous treatment for progressing DT that were not amenable to surgery or had refractory or recurrent DT after at least one line of therapy. Median subject age was 34 years, majority female (64%), with *CTNNB1* genetic mutation (61%), and extra-abdominal tumor-location (76%). The majority had received previous treatment (74%) with a median of two lines of previous therapy. Treatments included surgery (44%), radiation therapy (23%), chemotherapy (34%), and TKIs (33%) with sorafenib being the most common TKI received (24%). The primary outcome was progression-free survival (PFS). Secondary endpoints included objective response rate (ORR) and patient-reported outcomes. Results showed a statistically significant 71% reduction of disease risk progression in subjects who received nirogacestat (Ogsiveo) in 28-day cycles versus subjects who received placebo (hazard ratio [HR] = 0.29; $p < 0.001$). However, data is of low/uncertain value for clinical decision-making, as the primary and objective secondary outcomes are surrogate endpoints and are not validated to correlate with morbidity, mortality, quality of life, symptom, or functionality improvements. Although the study found statistically and clinically significant differences in favor of nirogacestat (Ogsiveo) compared to placebo in patient-reported outcomes at cycle 10, there remains uncertainty in whether clinically meaningful results were attained throughout the course of treatment as only cycle 10 data is reported.

Investigational or Not Medically Necessary Uses

- I. Nirogacestat (Ogsiveo) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Multiple myeloma
 - i. A phase 1b interventional study of belantamab mafodotin in combination with nirogacestat (Ogsiveo) and pomalidomide in patients with multiple myeloma is currently in the recruitment phase and is estimated to be completed by October of 2026. There is currently a lack of sufficient evidence or additional scientific literature to support the use of nirogacestat (Ogsiveo) in multiple myeloma.
 - B. Ovarian Cancer
 - i. A phase 2 interventional study of nirogacestat (Ogsiveo) in ovarian granulosa cell tumors is currently in the active phase and is expected to be completed by July of 2026. There is currently a lack of sufficient evidence or additional scientific literature to support the use of nirogacestat (Ogsiveo) in ovarian cancer.
 - C. Pediatrics and adolescents under the age of 18 years old
 - i. A phase 2 interventional study to evaluate the efficacy and safety of nirogacestat (Ogsiveo) in pediatric patients >12 months to 18 years of age is currently in the active phase and is expected to be completed by December of 2024. There is currently a lack of sufficient evidence or additional scientific literature to support the use of nirogacestat (Ogsiveo) in members <18 years of age.
 - D. Use of nirogacestat (Ogsiveo) in combination with other oncology therapy
 - i. There are currently no ongoing or active trials to study the use of nirogacestat (Ogsiveo) in combination with other oncology therapy. There is currently a lack of additional scientific literature to support the use of nirogacestat (Ogsiveo) in combination with other chemotherapy agents.

** 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. OGSIVEO. Prescribing Information. SpringWorks Therapeutics, Inc; 2023
2. Unapproved nirogacestat (Ogsiveo) Dossier. SpringWorks Therapeutics. May, 2023
3. Approved nirogacestat (Ogsiveo) Dossier. SpringWorks Therapeutics. December, 2023.
4. National Comprehensive Cancer Network. Soft Tissue Sarcoma (Version 3.2023). NCCN. Updated December 12, 2023. Accessed December 18, 2023. https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf
5. Gounder M, Ratan R, Alcindor T, et al. Nirogacestat, a γ -Secretase Inhibitor for Desmoid Tumors. *N Engl J Med*. 2023;388(10):898-912. doi:10.1056/NEJMoa2210140
6. Nieuwenhuis MH, Lefevre JH, Bülow S, et al. Family history, surgery, and APC mutation are risk factors for desmoid tumors in familial adenomatous polyposis: an international cohort study. *Dis Colon Rectum*. 2011;54(10):1229-1234. doi:10.1097/DCR.0b013e318227e4e8
7. Nooka AK, Weisel K, van de Donk NW, et al. Belantamab mafodotin in combination with novel agents in relapsed/refractory multiple myeloma: DREAMM-5 study design. *Future Oncol*. 2021;17(16):1987-2003. doi:10.2217/fon-2020-1269

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HEALTH

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8. Children's Oncology Group. A Study of a New Drug, Nirogacestat, for Treating Desmoid Tumors That Cannot be Removed by Surgery. Clinicaltrial.gov. December 11, 2019. Updated November 11, 2023. Accessed December 19, 2023. <https://clinicaltrials.gov/study/NCT04195399>

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
Multi-Targeted Tyrosine Kinase Inhibitors (Multi-TKI)	Desmoid Tumor

Policy Implementation/Update:

Action and Summary of Changes	Date
Removed mutational analysis requirement from diagnosis of desmoid tumors	03/2024
Policy created	02/2024

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP140

Description

Nitisinone (Nityr; Orfadin) competitively inhibits 4-hydroxyphenyl-pyruvate dioxygenase (4HPPD), an enzyme present early in the tyrosine degradation pathway, thereby preventing the accumulation of toxic metabolites.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
nitisinone (nitisinone)	2 mg capsule	Hereditary tyrosinemia type 1	2 mg/kg/day
	5 mg capsule		
	10 mg capsule		
nitisinone (Nityr)	2 mg tablet		
	5 mg tablet		
	10 mg tablet		
nitisinone (Orfadin)	2 mg capsule		
	5 mg capsule		
	10 mg capsule		
	20 mg capsule		
	4 mg/mL suspension		

Initial Evaluation

- I. Nitisinone (Nityr; Orfadin) may be considered medically necessary when the following criteria below are met:
 - A. Medication is prescribed by, or in consultation with, a provider who specializes in the treatment of genetic or metabolic disorders; **AND**
 - B. A diagnosis of **hereditary tyrosinemia type 1 (HT-1)** when the following are met:
 1. Elevated succinylacetone (SA); **AND**
 2. Documentation of baseline plasma tyrosine level; **AND**
 3. Treatment will be used in conjunction with a diet restricted in tyrosine and phenylalanine
- II. Nitisinone (Nityr; Orfadin) is considered investigational when used for all other conditions, including but not limited to:
 - A. Alkaptonuria

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through this health plan; **AND**
- II. Member is not established on therapy through the use of 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. biochemical and/or clinical response).

Supporting Evidence

- I. In patients with HT-1, tyrosine metabolism is interrupted due to a lack of the enzyme (fumarylacetoacetate hydrolase) needed in the last step of tyrosine degradation. Toxic metabolites of tyrosine, succinylacetoacetate (SAA) and succinylacetone (SA), accumulate and cause liver and kidney toxicity. Nitisinone (Nityr; Orfadin) competitively inhibits 4-hydroxyphenyl-pyruvate dioxygenase (4HPPD), an enzyme present early in the tyrosine degradation pathway, thereby preventing the build-up of the toxic metabolites SAA and SA.
- II. Nitisinone (Nityr; Orfadin) must be used in conjunction with a diet restricted in tyrosine and phenylalanine to prevent further increased tyrosine levels. Dose is titrated as needed based on biochemical and/or clinical response. If the biochemical response is satisfactory, the dosage should be adjusted only according to body weight gain. Dose should not be adjusted according to tyrosine concentration.
- III. Nitisinone (Nityr; Orfadin) should be started as early as possible (i.e. immediately after diagnosis of HT1 by blood or urine measurement of SA).
- IV. If the biochemical parameters (except plasma SA) have not normalized within one month of starting therapy, the dose should be increased to 1.5 mg/kg/day. The dose of nitisinone should be adjusted to completely suppress excretion of SA; however, it may take as long as three months for complete suppression of SA to occur. A dose of 2 mg/kg/day may be needed, especially in infants; although, this dose should be considered maximal. Monitoring of the nitisinone blood levels is recommended for dose adjustment and also to check adherence.

Investigational or Not Medically Necessary Uses

- I. Nitisinone (Nityr; Orfadin) has not been sufficiently evaluated in the following settings. Limited evidence is available; however, safety and efficacy have not been established for:
 - A. Alkaptonuria

References

1. Orfadin [Prescribing Information]. Waltham, MA: Sobi, Inc; May 2019.
2. Nityr [Prescribing Information]. Cambridge, United Kingdom: Cycle Pharmaceuticals Ltd.; November 2018.
3. UpToDate, Inc. Disorders of tyrosine metabolism. UpToDate [database online]. Waltham, MA. Last updated August 08, 2019 Available at: <http://www.uptodate.com/home/index.html>.

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Policy Implementation/Update:

Date Created	December 2019
Date Effective	December 2019
Last Updated	December 2019
Last Reviewed	12/2019

Action and Summary of Changes	Date

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP142

Description

Octreotide acetate (Sandostatin, Bynfezia Pen, Mycapssa) works by suppressing LH response to GnRH, decreasing splanchnic blood flow, and inhibiting the release of serotonin, gastrin, vasoactive intestinal peptide, secretin, motilin, and pancreatic polypeptide.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
octreotide acetate (generic, Sandostatin)	50 mcg/mL ampule, vial, syringe	Acromegaly	90 ampules, vials, syringes/30 days
		Metastatic carcinoid tumor	
		Vasoactive intestinal peptide tumor (VIPoma)	
	100 mcg/mL ampule, vial, syringe	Acromegaly	
		Metastatic carcinoid tumor	
		Vasoactive intestinal peptide tumor (VIPoma)	
	500 mcg/mL ampule, vial, syringe	Acromegaly	
		Metastatic carcinoid tumor	
		Vasoactive intestinal peptide tumor (VIPoma)	
	1000mcg/5mL (200 mcg/mL) vial	Acromegaly	9 vials/30 days
		Metastatic carcinoid tumor	23 vials/30 days
		Vasoactive intestinal peptide tumor (VIPoma)	14 vials/30 days
octreotide acetate (Bynfezia Pen)	5000mcg/5mL (1000 mcg/mL) vial	Acromegaly	2 vials/30 days
		Metastatic carcinoid tumor	5 vials/30 days
		Vasoactive intestinal peptide tumor (VIPoma)	3 vials/30 days
octreotide acetate (Bynfezia Pen)	7000mcg/2.8mL (2500 mcg/mL) prefilled injection pen	Acromegaly	2 pens/30 days
		Metastatic carcinoid tumor	4 pens/30 days
		Vasoactive intestinal peptide tumor (VIPoma)	2 pens/30 days
octreotide acetate (Mycapssa)	20 mg capsule	Acromegaly	112 capsules/28 days
Provider Administered Agents*			

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octreotide acetate, mi-spheres (Sandostatin LAR)	10 mg vial	Acromegaly; Metastatic carcinoid tumor; Vasoactive intestinal peptide tumor (VIPoma)	N/A
	20 mg vial		
	30 mg vial		

**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

- I. **Octreotide acetate (Sandostatin, Bynfezia Pen, Mycapssa) and generic octreotide acetate** may be considered medically necessary when the following criteria below are met:
 - A. Member is 18 years of age or older; **AND**
 - B. If requesting injectable brand octreotide acetate (Sandostatin, Bynfezia Pen): Treatment with generic octreotide has been ineffective, not tolerated, or is contraindicated; **AND**
 - C. A diagnosis of one of the following:
 1. **Acromegaly; AND**
 - i. Member has had inadequate response to, or cannot be treated with surgical resection and pituitary irradiation; **AND**
 - ii. If requesting oral octreotide acetate (Mycapssa): member has a documented response and tolerability to treatment with long-acting octreotide injection (Sandostatin LAR) OR lanreotide (Somatuline Depot) injection; **AND**
 - a. Provider rationale as to why continuation of therapy with long-acting octreotide injection (Sandostatin LAR) OR lanreotide (Somatuline Depot) injection is not appropriate (i.e., there is medical necessity for change outside of patient preference); **OR**
 2. **Metastatic carcinoid tumor; AND**
 - i. Use is intended for the symptomatic management of severe diarrhea and/or flushing episodes; **AND**
 - ii. The request is for injectable octreotide (e.g. generic octreotide acetate, Sandostatin, Bynfezia Pen); **OR**
 3. **Vasoactive intestinal peptide tumors (VIPomas)** [pancreatic neuroendocrine (islet cell) tumor, insulinoma, glucagonoma, somatostatinoma, and gastrinoma]; **AND**
 - i. Use is intended for the symptomatic management of profuse watery diarrhea; **AND**
 - ii. The request is for injectable octreotide (e.g. generic octreotide acetate, Sandostatin, Bynfezia Pen); **AND**
- II. Octreotide (Sandostatin, Sandostatin LAR, Bynfezia Pen) is considered investigational when used for all other conditions.
- III. Octreotide oral capsules (Mycapssa) are considered investigational when used for all other conditions, including but not limited to, metastatic carcinoid tumor and vasoactive intestinal peptide tumors (VIPomas).
 - A. Octreotide capsules (Mycapssa) have only been studied and FDA-approved in the setting of long-term maintenance of acromegaly symptoms and is therefore considered

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investigational when used for all other indications, including metastatic carcinoid tumors and VIPomas.

Renewal Evaluation

- I. Disease response with improvement in patient's symptoms including reduction in symptomatic episodes (such as diarrhea, rapid gastric dumping, flushing), and/or stabilization of glucose levels, and/or decrease in size of tumor or tumor spread; **OR**
- II. For **acromegaly** ONLY: Disease response as indicated by an improvement in signs and symptoms compared to baseline; **AND**
 - 1. Age-adjusted normalization of serum IGF-1; **OR**
 - 2. Reduction of growth hormone (GH) by random testing to < 1.0 mcg/L

Supporting Evidence

- I. The 2014 Endocrine Society Practice Guidelines for Acromegaly recommend transsphenoidal surgery/surgical resection/debulking as primary therapy for Acromegaly patients, followed by radiation therapy for residual tumor mass following surgery. In patients with persistent disease following surgery, guidelines recommend use of somatostatin receptor ligands (SRLs) or pegvisomant as the initial adjuvant medical therapy.
- II. Bynfezia Pen was approved via the 505 (b)(2) pathway and relies on the FDA's finding of safety and effectiveness for the previously approved drug Sandostatin (octreotide acetate injection). The FDA has found that Bynfezia Pen and Sandostatin are pharmacokinetically bioequivalent based on data from the comparative PK study submitted with the NDA. The FDA expects the benefits and risks of Bynfezia pen used at the proposed doses will be similar to the benefits and risks associated with Sandostatin for the treatment of acromegaly, severe diarrhea/flushing episodes associated with metastatic carcinoid tumors, and profuse watery diarrhea associated with Vasoactive Intestinal Peptide (VIPoma) secreting tumors.
- III. Octreotide acetate oral capsules (Mycapssa) was approved for the treatment of Acromegaly ONLY by the FDA based on data from the randomized, double-blind, placebo controlled, phase 3 CHIASMA OPTIMAL study in Acromegaly patients who were previously treated with stable doses of long-acting SRLs (octreotide or lanreotide). The primary endpoint was the proportion of patients maintaining biochemical response, defined as $\text{IGF-1} \leq 1.0 \times \text{ULN}$, studied in a population of adult patients age 18 and older who had evidence of active acromegaly disease and had an average IGF-1 of $\leq 1.0 \times \text{ULN}$ on a stable dose of injectable octreotide or lanreotide. The primary endpoint was met, as 58% of patients receiving oral octreotide capsules maintained IGF-1 response versus the 19% receiving placebo ($P=0.008$). Octreotide acetate oral capsules (Mycapssa) were safe and well tolerated. No new or unexpected significant safety signals were observed during the trial. In the absence of head to head studies, long acting injectables remain the best value treatment for acromegaly and are preferred unless there is medical necessity for the oral product.

References

1. Sandostatin [package insert]. East Hanover, NJ; Novartis Pharmaceuticals Corporation; April 2019.
2. Melmed, S. Treatment of acromegaly. In; UpToDate. Martin, KA (Ed), UpToDate, Waltham, MA, 2019
3. Mycapssa [package insert]. Needham, MA: Chiasma, Inc.; June 2020.
4. Bynfezia Pen [package insert]. Cranbury, NJ; Sun Pharmaceutical Industries, Inc.; January 2020.
5. Bynfezia Pen [FDA Medical Review]. Center for Drug Evaluation and Research: Summary Review. 15 Jan 2020. Accessed from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/213224Orig1s000SumR.pdf
6. Samson SL, Nachtigall LB, Flaseriu M, et al. Results from the phase 3, randomized, double-blind, placebo-controlled Chiasma Optimal study of oral octreotide capsules in adult patients with acromegaly. J Endocr Soc. 2020;4(suppl 1).
7. Katznelson L, Laws ER, Melmed S, et al. Acromegaly: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab, November 2014, 99(11):3933-3951.

Policy Implementation/Update:

Action and Summary of Changes	Date
Added Bynfezia Pen to policy with requirement for inadequate response to <u>generic</u> octreotide, unless not tolerated or contraindicated. Mycapssa capsules added in the setting of acromegaly requiring response with long acting octreotide injection or lanreotide (Somatuline Depot) injection; and requiring rationale for use of oral formulation over continuation of injectable long acting product. Removed trial and failure of bromocriptine from requirements for approval of injectable octreotide for acromegaly. Updated quantity limits of all products to align with diagnosis.	9/2020
Transitioned to policy format and updated the following: • Added age requirement of 18 years or older • For octreotide (Sandostatin), added requirement for inadequate response to <u>generic</u> octreotide, unless not tolerated or contraindicated • Removed octreotide (Sandostatin LAR) from the policy as it is excluded from coverage under the pharmacy benefit	12/2019
Previous review	10/2017
Criteria created	10/2016

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP048

Split Fill Management*

Description

Olaparib (Lynparza) is an orally administered poly (ADP-ribose) polymerase (PARP) enzymes inhibitor including PARP1, PARP2, and PARP3. PARP enzymes are involved in normal cellular homeostasis, such as DNA transcription, cell cycle regulation, and DNA repair.

Length of Authorization

- Initial:
 - i. Early, high-risk breast cancer: 12 months
 - ii. All other indications: 3 months
- Renewal:
 - i. Early, high-risk breast cancer: no renewals allowed
 - ii. All other indications: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
olaparib (Lynparza)	Breast cancer, early, high-risk, HER2-negative, germline BRCA-mutated (gBRCAm), after neoadjuvant or adjuvant chemotherapy; Breast cancer, metastatic, HER2-negative, gBRCAm with prior chemotherapy in the metastatic setting; Ovarian, fallopian tube, or primary peritoneal cancer; advanced, homologous recombination deficient (HRD)-positive status; after complete or partial response to first-line platinum chemotherapy, in combination with bevacizumab; maintenance therapy;	100 mg tablets	120 tablets/30 days

	Ovarian, fallopian tube, or primary peritoneal cancer; gBRCAm or sBRCAm, after first-line platinum-based chemotherapy, first-line maintenance therapy; Ovarian, fallopian tube, or primary peritoneal cancer; recurrent after complete or partial response to platinum-based chemotherapy; maintenance therapy Pancreatic adenocarcinoma, metastatic gBRCAm or sBRCAm; first-line maintenance therapy in those who have not progressed on at least 16 weeks of first-line platinum-based chemotherapy; Prostate cancer, metastatic castration-resistant, homologous recombination repair (HRR) gene-mutated Prostate cancer, metastatic castration-resistant, deleterious or suspected deleterious BRCA-mutated (BRCAm)	150 mg tablets	120 tablets/30 days

Initial Evaluation

- I. **Olaparib (Lynparza)** may be considered medically necessary when the following criteria below are met:
 - A. Prescribed by, or in consultation with, a specialist in oncology; **AND**
 - B. The patient has not progressed on or after prior PARP inhibitor therapy (e.g., olaparib [Lynparza], niraparib [Zejula], rucaparib [Rubraca], talazoparib [Talzenna]); **AND**
 - C. A diagnosis of one of the following:
 1. **Ovarian cancer (including fallopian tube and primary peritoneal cancer); AND**
 - i. The member has advanced or metastatic (Stage III-IV) disease; **AND**
 - ii. Request is for maintenance therapy; **AND**
 - a. Member has completed a prior platinum-based chemotherapy regimen (e.g., cisplatin, carboplatin, oxaliplatin); **AND**
 - b. The tumor is platinum-sensitive (i.e., the patient is in complete or partial response to their most recent platinum-based regimen); **AND**
 - c. Documentation of deleterious (pathogenic) or suspected deleterious (likely pathogenic) BRCA mutations (gBRCAm or sBRCAm); **AND**
 - i. For first-line maintenance therapy:
 1. Olaparib (Lynparza) will be used as monotherapy; **AND**
 - a. Member has not received prior treatment with bevacizumab; **OR**

2. Member has received, and currently has a positive response to bevacizumab treatment; **AND**
 - a. Documentation of deleterious (pathogenic) or suspected deleterious (likely pathogenic) homologous recombination deficient-positive mutation (gHRDm); **AND**
 - b. Olaparib (Lynparza) will continue to be used in combination with bevacizumab; **OR**
 - ii. Request is for maintenance therapy for recurrent disease after at least two prior lines of platinum-based (e.g., cisplatin, carboplatin, oxaliplatin) chemotherapy regimens
2. **Breast cancer, early, high-risk or metastatic; AND**
 - i. Member has a diagnosis of HER2-negative breast cancer; **AND**
 - ii. Documentation of deleterious (pathogenic) or suspected deleterious (likely pathogenic) gBRCAm; **AND**
 - iii. Diagnosis of early (stage II-III) breast cancer; **AND**
 - a. Provider attestation that member is at high risk of disease recurrence; **AND**
 - b. Has required surgical intervention; **AND**
 - c. Has received prior adjuvant or neoadjuvant therapy with a taxane (e.g., docetaxel), an anthracycline (e.g., doxorubicin), or platinum-based chemotherapy (e.g., cisplatin, carboplatin, oxaliplatin); **AND**
 - d. Olaparib (Lynparza) will be used as monotherapy or in combination with endocrine therapy (e.g., anastrozole, tamoxifen, fulvestrant); **OR**
 - iv. Diagnosis of metastatic (stage IV) breast cancer; **AND**
 - a. Has received prior treatment with an anthracycline (e.g., doxorubicin); **AND**
 - b. Has received prior treatment with a taxane (e.g., paclitaxel); **AND**
 - c. Member has disease progression on at least one prior endocrine therapy; **OR**
 - i. Endocrine therapy has been deemed inappropriate by the treating healthcare provider; **AND**
 - d. Medication will not be used in combination with other anti-cancer agents; **OR**
3. **Pancreatic cancer, First-line Maintenance; AND**
 - i. Documentation of deleterious (pathogenic) or suspected deleterious (likely pathogenic) gBRCAm; **AND**
 - ii. Diagnosis of metastatic pancreatic adenocarcinoma; **AND**
 - iii. The member has received at least 16 weeks of continuous treatment with a platinum-based chemotherapy regimen (e.g., cisplatin, carboplatin, oxaliplatin) that was administered as first-line therapy; **AND**

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- iv. Provider attests that the disease has not progressed while on first-line platinum-based chemotherapy regimen (e.g., cisplatin, carboplatin, oxaliplatin); **AND**
- v. Medication will not be used in combination with other anti-cancer agents;
OR
- 4. **Prostate cancer, metastatic, castration-resistant (mCRPC); AND**
 - i. Documentation of metastatic disease (i.e., stage IV); **AND**
 - ii. Disease is castration-resistant, defined by disease progression despite ongoing therapy with a gonadotropin-releasing hormone analog (GnRH) or a bilateral orchiectomy; **AND**
 - iii. The request is for olaparib (Lynparza) in combination with abiraterone (Zytiga, Yonsa) and prednisone or prednisolone (Note: the plan's preferred therapy is generic abiraterone unless contraindicated or not tolerated);
AND
 - a. The member has not had disease progression on a second-generation antiandrogen agent (e.g., abiraterone (Zytiga, Yonsa), enzalutamide (Xtandi), apalutamide (Erleada), darolutamide (Nubeqa)); **AND**
 - b. Documentation of deleterious (pathogenic) or suspected deleterious (likely pathogenic) gBRCAm; **OR**
 - iv. The request is olaparib (Lynparza) monotherapy; **AND**
 - a. Documentation of deleterious (pathogenic) or suspected deleterious (likely pathogenic) alteration in at least one of the following HRR genes: ATM, BRCA1, BRCA2; **AND**
 - b. Disease has progressed on prior enzalutamide (Xtandi) or abiraterone (Zytiga, Yonsa) treatment.
- II. Olaparib (Lynparza) is considered investigational when used for all other conditions, including but not limited to:
 - A. Early breast cancer with low-moderate-risk without metastasis, and/or HER2-positive, and/or breast cancer without gBRCAm
 - B. Treatment of early, high-risk breast cancer for > 12 months
 - C. Pancreatic cancer without metastasis, and without gBRCAm
 - D. Metastatic, gBRCAm pancreatic cancer that has progressed on first line platinum-based chemotherapy
 - E. Metastatic, castration-resistant prostate cancer with a tumor mutation NOT listed above (including BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, or RAD54L) when used as a subsequent-line treatment
 - F. Use after disease progression on or after prior PARP inhibitor therapy
 - G. Treatment of advanced ovarian cancer after 3 or 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. Olaparib (Lynparza) will not be used in combination with other anti-cancer agents (outside of gonadotropin-releasing hormone agonist [e.g., leuprolide] or endocrine therapy [e.g., anastrozole, tamoxifen, fulvestrant] or bevacizumab or abiraterone); **AND**
- IV. Clinical documentation of response to treatment (e.g., stabilization of disease or decrease in tumor size, or tumor spread).

Supporting Evidence

- I. Many treatment options exist for ovarian, breast, pancreatic, and prostate cancer. Initial and subsequent therapies in this setting are contingent upon patient-specific characteristics. Given the complexities surrounding the diagnosis and treatment options, targeted drug therapies, such as PARP inhibitors, should be prescribed by, or in consultation with, an oncologist.
- II. 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 the progression of disease on another PARP inhibitor.
- III. **Treatment of Ovarian Cancer:**
 - In the pivotal trials for maintenance treatment of recurrent ovarian cancer and first-line maintenance therapy for ovarian cancer with gBRCAm or sBRCAm, eligible patients had completed at least ONE course of platinum-based chemotherapy. In the pivotal trials for first-line maintenance therapy for ovarian cancer with gBRCAm or sBRCAm non-eligible patients included: patients with early-stage disease (FIGO State I, IIA, IIB, or IIC) and patients with prior bevacizumab treatment. Subjects were randomized to treatment allocation 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 eight weeks as possible), to ensure the member is platinum-sensitive.
 - PAOLA-1, the Phase 3 trial that studied olaparib (Lynparza) as dual therapy with bevacizumab for maintenance therapy for advanced ovarian cancer, was a double-blind, randomized, placebo-controlled trial with the primary endpoint of progression free survival (PFS). The primary endpoint results of the predefined subgroups of HRD-positive, HRD-negative, or unknown found only a statistically significant difference in PFS in the HRD-positive subjects (HR: 0.33, 95% CI: 0.25, 0.45) and not the HRD-negative or unknown patients (HR: 0.92, 95% CI: 0.72, 1.17). Subjects enrolled in the trial had Stage III or IV disease and had a successful response to prior taxane-based chemotherapy.
 - The NCCN guideline for the treatment of ovarian cancers, recommends pathological staging followed by cytoreductive surgery as the preferred first-line treatment option for early-stage non-metastatic ovarian cancer. For patients who are poor candidates for surgery or

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have a low likelihood of optimal cytoreduction, a neoadjuvant systemic therapy (e.g., paclitaxel and platinum-based chemotherapy, bevacizumab) may be required. Similarly, these chemotherapy regimens may be applicable as adjuvant therapy following cytoreductive surgery (for stage II-IV disease). Post-primary treatment, a first-maintenance therapy with PARP inhibitors (e.g., niraparib, olaparib) may be utilized to extend remission. For a disease that recurs after first-maintenance, recurrence therapy with platinum-based chemotherapy regimens followed by a PARP inhibitor for maintenance (also known as recurrent maintenance) may be warranted. Use of olaparib (Lynparza) for recurrent-maintenance is recommended only for patients, who have not previously been treated with a PARP inhibitor.

IV. **Treatment of Breast Cancer:**

- OlympiA was a 12-month phase 3, double-blinded, randomized, placebo-controlled trial that investigated the use of olaparib in patients with early, high-risk, non-metastatic breast cancer with documented germline BRCA mutations (gBRCAm) that is predicted to be deleterious or suspected deleterious without disease progression after neoadjuvant or adjuvant treatment with anthracycline, taxane, or platinum agents. Additional oncology therapy was not permitted, but concomitant endocrine therapy was allowed. High-risk patients were defined by residual invasive disease after neoadjuvant therapy, or positive histopathological tests showing affected axillary or lymph nodes after adjuvant therapy. The primary end point was invasive disease-free survival (IDFS), defined as time to first invasive breast tumor, invasive disease, disease recurrence, second primary invasive cancer, or death from any cause. Three-year IDFS was present in 85.9% of the olaparib arm and 77.1% in the placebo arm (HR = 0.58, [95% CI 0.41, 0.82], p=0.001). Overall survival was greater in the olaparib group by 32% compared to placebo (HR = 0.68, [98.5% CI 0.47-0.97], p=0.009). Distant disease-free survival was significantly longer among patients assigned to receive olaparib than placebo: 87.5% vs 80.4% (HR = 0.57, [99.5% CI, 0.39 to 0.83], P<0.001).
 - i. In line with the duration of the OlympiA trial, the FDA approved olaparib for treatment of HER2-negative high-risk, early breast cancer for up to 12 months, or until disease recurrence, or unacceptable toxicity. NCCN guidelines similarly recommend olaparib be used for up to 12 months.
 - ii. Since the publication of the OlympiA trial, capecitabine has been added as another guideline-directed adjuvant therapy option for HER2-negative, triple negative breast cancer (TNBC). Other guideline recommended adjuvant therapy options include olaparib (Lynparza) and pembrolizumab. Currently, there are no data to guide selection or sequencing of adjuvant therapy (olaparib or capecitabine) in HER2-negative TNBC. However, selection of therapy is based on patient specific factors (e.g., presence of gBRCAm for Lynparza). Current utilizers of capecitabine as an adjuvant therapy may be expected to transition to Lynparza based on presence of high-risk breast cancer, gBRCAm, and patient-specific factors including tolerability and toxicity. Additionally, the OlympiAD trial for metastatic breast cancer supported the efficacy of Lynparza versus chemotherapy (45% of patients received capecitabine) via improved surrogate outcomes of PFS.

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- In the pivotal trial for breast cancer with metastatic, HER2-negative and gBRCAm, eligible patients had received neoadjuvant, adjuvant, or treatment for metastatic disease with an anthracycline (unless it was contraindicated) and a taxane. Approximately 70% of patients had received treatment in the metastatic setting; with 27% of patients having progressed after two lines of systemic therapies in the metastatic setting. 33% had no prior systemic therapy for metastatic disease. Eligible patients in this trial could have hormone-receptor positive metastatic breast cancer (i.e., estrogen-receptor positive, progesterone-receptor positive, or both) or triple negative metastatic breast cancer. Patients with hormone-receptor positive disease had received at least one endocrine therapy (adjuvant therapy or therapy for metastatic disease) and had disease progression during therapy, unless they had disease for which endocrine therapy was considered to be inappropriate.

V. **Treatment of Pancreatic Cancer:**

- The pivotal trial (POLO) is a Phase 3 trial that studied metastatic, gBRCAm pancreatic cancer; eligible patients had received a minimum of 16 weeks of first-line platinum-based chemotherapy (cisplatin, carboplatin, or oxaliplatin) and had not progressed while on the first-line platinum-based chemotherapy. The patients were randomized in a 3:2 ratio to receive maintenance olaparib (Lynparza) or placebo with the primary end point progression-free survival. The median progression-free survival was statistically significant, 7.4 months in the olaparib (Lynparza) arm compared to 3.8 months in the placebo arm (HR 0.53 [95% CI, 0.35-0.81], $p=0.0035$). The interim analysis of overall survival showed no difference between groups (median, 18.9 months vs. 18.1 months; hazard ratio for death, 0.91; 95% CI, 0.56 to 1.46; $P=0.68$). Additionally, there was no significant between-group differences in health-related quality of life.
- Limited exception should be granted to those who do not meet the criteria for metastatic, gBRCAm pancreatic cancer as stated in this policy, given the current lack of data to support an improvement in survival or quality of life even in the evaluated population.
- The preferred systemic regimens for metastatic, gBRCAm pancreatic cancer include:
 - i. FOLFIRINOX or modified FOLFIRINOX $\pm$ subsequent chemoradiation
 - ii. Gemcitabine + albumin-bound paclitaxel $\pm$ subsequent chemoradiation

VI. **Treatment of Prostate Cancer:**

- PROfound, the Phase 3 trial that studied olaparib (Lynparza) in metastatic castration-resistant prostate cancer, enrolled men with homologous recombination repair (HRR) gene mutations in at least one of 15 prespecified HRR genes. Eligible patients had either a history of bilateral orchiectomy or were using luteinizing hormone-releasing hormone (LHRH) analog therapy and had progressed on enzalutamide or abiraterone acetate or both and were randomized (2:1) to receive either olaparib (Lynparza) or investigator's choice of enzalutamide or abiraterone acetate. Subjects were assigned cohorts based on HRR mutation (Cohort A: ATM, BRCA1, BRCA2; Cohort B: BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, or RAD54L). The primary endpoint was PFS in Cohort A and was significant between the treatment groups (HR: 0.34, 95% CI: 0.25, 0.47; $p<0.001$). Additionally, OS in Cohort A was significantly different between treatment groups (HR: 0.69, 95% CI: 0.50, 0.97; $p=0.0175$). PFS and OS were studied in Cohort B as exploratory endpoints and the results were not statistically significant and did not suggest improved outcomes with olaparib (Lynparza) over abiraterone or enzalutamide in those patients.

- 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.

Investigational or Not Medically Necessary Uses

- I. Early breast cancer with low to moderate-risk without metastasis, and/or HER2-positive, and/or breast cancer without gBRCAm, and/or use of Lynparza >1 year for early, high-risk breast cancer
 - A. Safety and efficacy have only been established in patients with high-risk, non-metastatic HER2-negative, gBRCAm breast cancer treated with olaparib for a maximum duration of 12 months.
- II. Pancreatic cancer without metastasis, and without gBRCAm
 - A. The safety and efficacy of olaparib in the pancreatic cancer setting have only been established in patients with metastatic disease with gBRCAm who has not progressed on the first-line platinum-based chemotherapy.
- III. Metastatic, gBRCAm pancreatic cancer that has progressed on first-line platinum-based chemotherapy
 - A. The safety and efficacy of olaparib in the pancreatic cancer setting have only been established in patients with metastatic disease with gBRCAm who has not progressed on the first-line platinum-based chemotherapy.
- IV. Use after disease progression on, or after, prior PARP inhibitor therapy
 - A. There is no evidence to support the use of a subsequent PARP inhibitor following the progression of disease on another PARP inhibitor.
- V. Metastatic castration-resistant prostate cancer with other tumor mutations (including BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, or RAD54L)
 - A. The phase 3 trial PROfound studied olaparib (Lynparza) versus enzalutamide or abiraterone in Cohort A (ATM, BRCA1, BRCA2) and Cohort B (BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, or RAD54L). While statistically significant differences in PFS and overall survival (OS) were found in treatment with olaparib (Lynparza) in Cohort A and pooled Cohort A+B, the same was not found in Cohort B alone. Exploratory endpoints found PFS in Cohort B (HR: 0.88; 95% CI: 0.58, 1.36) and OS in Cohort B (HR: 0.73; 95% CI: 0.45, 1.23) not to be

statistically significant and does not indicate improved patient outcomes with use of olaparib (Lynparza) over enzalutamide or abiraterone in these patients.

VI. Treatment of advanced ovarian cancer after 3 or more lines of therapy

- A. The manufacturer of olaparib (Lynparza) voluntarily withdrew the indication for treatment of adult patients with advanced ovarian 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. Including, a subgroup analysis indicating a potential detrimental effect on overall survival (OS) for Lynparza compared to the chemotherapy control arm in the subgroup of patients who had received three or more prior lines of chemotherapy corresponding to the scope of the treatment indication for Lynparza in the randomized Phase III study, SOLO3 (NCT02282020).
- B. SOLO3 was requested by the FDA to confirm the clinical benefit of Lynparza in the above indication. SOLO3 is a Phase III, open-label, randomized, controlled, multi-center study to assess the efficacy and safety of single agent Lynparza vs standard of care, based on physician's choice of single agent chemotherapy (i.e., weekly paclitaxel, topotecan, pegylated liposomal doxorubicin [PLD], or gemcitabine) in patients with platinum-sensitive relapsed (PSR) ovarian cancer who had received at least 2 prior lines of platinum-based chemotherapy, and who carried a germline deleterious or suspected deleterious breast cancer susceptibility gene (BRCA1/2) mutation. SOLO3 met its primary endpoint of ORR and the key secondary endpoint of progression-free survival (PFS). The final OS analysis subsequently occurred in 2021. In a OS subgroup analysis, a potential survival detriment was observed in the subgroup of patients treated with 3 or more prior lines of chemotherapy.

** 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. Lynparza [Prescribing Information]. Wilmington, DE: AstraZeneca Pharmaceuticals. August 2022.
2. Kaufman, B, Shapira-Frommer, R, Schmutzler, RK, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. *J Clin Oncol*. 2015 Jan; 33(3):244-50. PMID 25366685.
3. Robson, M, Im, S, Senkus, E, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. *N Engl J Med*. 2017 Aug; 377(6):523-533. PMID: 28578601.
4. Tutt ANJ, Garber JE, Kaufman B, et al. Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer. *N Engl J Med*. 2021 Jun 24;384(25):2394-2405.
5. *Lynparza Reduced Risk of Death by 32% in the Adjuvant Treatment of Patients with Germline BRCA-Mutated High-Risk Early Breast Cancer*. AstraZeneca; 2022. <https://www.astrazeneca.com/media-centre/press-releases/2022/lynparza-reduced-risk-of-death-by-32-percent-in-the-adjuvant-treatment-of-patients-with-germline-brca-mutated-high-risk-early-breast-cancer.html>. Accessed April 20, 2022
6. Masuda N, Lee SJ, Ohtani S, Im YH, Lee ES, Yokota I, et al. Adjuvant Capecitabine for breast Cancer after preoperative chemotherapy. *N Engl J Med*. 2017;376(22):2147–59.

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7. Ledermann J, Harter P, Gourley M, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med*. 2012 Apr; 366(15):1382-92. PMID 22452356.
8. Pukade-Lauraine E, Ledermann J, Selle F, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation 9SOLO2/ENGOT-Ov21): a double-blind, randomized, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2017 Sep 18(9):1274-1284. PMID: 28754483.
9. NCCN Clinical Practice Guidelines in Oncology™. Ovarian Cancer v.5.2017. [cited 2/23/2018]; Available from: https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf
10. NCCN Clinical Practice Guidelines in Oncology™. Breast Cancer v.2.2022. [cited 4/18/2022]; Available from: https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
11. NCCN Clinical Practice Guidelines in Oncology™. Pancreatic Adenocarcinoma v.1.2020. [cited 01/29/2020]; Available from: https://www.nccn.org/professionals/physician_gls/pdf/pancreatic_blocks.pdf
12. Golan T, Hammel P, Reni M, et al. Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer. *N Engl J Med*. 2019 July; 381:317-327. DOI: 10.1056/NEJMoa1903387
13. de Bono J, Mateo J, et al. Olaparib for Metastatic Castration-Resistant Prostate Cancer. *N Engl J Med*. 2020 May 28;382(22):2091-2102. doi: 10.1056/NEJMoa1911440.
14. Ray-Coquard I, Pautier P, et al. Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. *N Engl J Med*. 2019 Dec 19;381(25):2416-2428. doi: 10.1056/NEJMoa1911361.

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
Cyclin-Dependent Kinase (CDK) 4/6 Inhibitors	Breast cancer
Talazoparib (Talzenna)	Breast cancer
Niraparib (Zejula)	Ovarian Cancer
Rucaparib (Rubraca)	Ovarian Cancer
Gonadotropin-releasing hormone (GnRH)	Advanced prostate cancer
	Advanced breast cancer in premenopausal women
	Reduction of endometrial thickness prior to endometrial ablation
	Gender dysphoria
	Central Precocious Puberty (CPP)
	Uterine leiomyoma (fibroids)
darolutamide (Nubeqa), apalutamide (Erleada), enzalutamide (Xtandi), abiraterone (Zytiga, Yonsa)	Endometriosis
	Prostate cancer

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. Added requirement of deleterious or suspected deleterious BRCA-mutated (BRCAm) for the treatment of mCRPC in combination with abiraterone.	09/2023
Added expanded indication for the treatment of mCRPC in combination with abiraterone; updated supporting evidence	06/2023
Removal of ovarian cancer indication in the late line (3+) treatment setting following voluntarily withdraw of the indication by the manufacturer.	09/2022
Defined castration resistant disease in setting of prostate cancer. Updated ovarian cancer criteria to align with FDA approved indications and to remove redundancies in coverage requirements; updated breast cancer criteria to remove requirement of 'no more than 2 therapies in metastatic setting'; updated supporting evidence	08/2022

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Added new FDA expanded indication as an adjuvant therapy in early, high-risk, non-metastatic breast cancer. Combined criteria for metastatic and early, high-risk breast cancer. Updated investigational section and supporting evidence. Added criteria to disallow use after progression on another PARP inhibitor to align with other PARP inhibitor policies. Added renewal criteria to disallow combination therapy to align with initial criteria. Added related policies table.	06/2022
Included new FDA expanded indications as first-line maintenance therapy in advanced HRD-positive ovarian cancer in combination with bevacizumab and metastatic castration-resistant prostate cancer with certain HRR mutations. Supporting evidence has been included in the policy.	10/2020
Included new FDA expanded indication as first-line maintenance therapy in pancreatic adenocarcinoma with metastasis, gBRCAm, and patients whose disease has not progressed on at least 16 weeks of a first-line platinum-based chemotherapy regimen. The criteria for approval in the pancreatic adenocarcinoma setting is to label, and the supporting evidence has been included in this policy. Advanced ovarian cancer without gBRCAm has been removed from the investigational and experimental section since olaparib (Lynparza) is approved in ovarian cancer without gBRCAm or sBRCAm. Pancreatic cancer without gBRCAm, and pancreatic cancer that has progressed on platinum-based chemotherapy have been added to the investigational and experimental section with supporting evidence. To improve clarity, for all the indications in this policy, the mutation documentation and the specific diagnoses have been separated out into individual criterion. Removal of toxicity question upon renewal as this is managed by the provider.	02/2020
Removal of DDID to reflect the most updated template version, removed the 8 weeks criterion around most recent platinum-based therapy in the setting of maintenance therapy in ovarian cancer; in place of the 8 weeks criterion, provider attestation and documentation is required instead.	12/2019
Criteria transitioned to policy format with the following additional updates: Included new FDA expanded indication as first-line maintenance therapy in ovarian cancer with gBRCAm or sBRCAm after complete or partial response to platinum-based chemotherapy. Additionally, a question was added to the renewal portion of this policy to assess for toxicity. Capsule formulation is no longer available; therefore, it has been removed from policy. Lastly, NCCN recognizes the term “deleterious” as pathogenic in the setting of gBRCAm OR sBRCAm; therefore, the policy has been updated to include the term “pathogenic” and “likely pathogenic” in parentheses next to the terms “deleterious” and “suspected deleterious” respectively.	03/2019
Criteria update: Added coverage criteria for ovarian cancer maintenance and metastatic breast cancer	02/2018

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP323

Description

Olezarsen (Tryngolza) is a conjugated antisense oligonucleotide that is administered subcutaneously.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
olezarsen (Tryngolza)	Adjunct to diet to reduce triglycerides in adults with familial chylomicronemia syndrome (FCS)	80 mg/0.8 mL autoinjector	0.8 mL/30 days

Initial Evaluation

- I. **Olezarsen (Tryngolza)** 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, endocrinologist, gastroenterologist, or provider that specializes in the treatment of lipid disorders (e.g., lipidologist); **AND**
 - C. A diagnosis of **familial chylomicronemia syndrome (FCS)** when the following are met:
 1. Documentation of biallelic pathogenic variants in at least one gene causing familial chylomicronemia syndrome (FCS) (e.g., LPL, GP1HBP1, APOA5, APOC2, or LMF1); **OR**
 - i. Documentation of a score ≥ 45 on the North American FCS (NAFCS); **AND**
 2. Documentation member has a fasting triglyceride level greater than, or equal to, 880 mg/dL; **AND**
 3. Provider attestation member has a history of pancreatitis; **AND**
 - D. Provider attestation that the use of traditional lipid lowering medications (e.g., statin, fibrate, omega-3 fatty acid, etc.) has been ineffective in lowering fasting triglyceride level; **AND**
 - E. Provider attestation olezarsen (Tryngolza) will be used in combination with a low-fat diet (i.e., no more than 20 g of total fat per day)
- II. Olezarsen (Tryngolza) is considered investigational when used for all other conditions, including but not limited to:
 - A. Hypertriglyceridemia

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 member has exhibited a reduction in fasting triglyceride level from baseline; **AND**
- IV. Provider attestation medication will be used in combination with a low-fat diet (i.e., no more than 20 g of fat per day)

Supporting Evidence

- I. Familial chylomicronemia syndrome (FCS) is a rare genetic disorder characterized by the body's inability to efficiently break down triglycerides due to a lack of functional lipoprotein lipase (LPL), leading to extremely elevated serum triglyceride levels. Diagnosis is confirmed by genetic testing showing the presence of biallelic pathogenic variants FCS-causing genes (e.g., LPL, GP1HBP1, APOA5, APOC2, or LMF1). All genetic variants responsible for FCS have not yet been discovered and there are a significant portion of patients with FCS that have indeterminate genetic results due to uncertain variants (ranges from 20-40%). Foundational organizations have been more accepting of confirmed FCS via a NAFCS score of ≥ 45 .
- II. Symptoms of FCS include frequent abdominal pain, episodes of acute pancreatitis, nausea/vomiting, and presence of xanthomas and/or lipemia retinalis. Traditional medications used to lower triglycerides are often ineffective in this population. Currently, FCS is managed through dietary intake (less than 20 g of fat intake daily) and other lifestyle interventions (e.g., exercise, avoidance of alcohol, etc.). Olezarsen (Tryngolza) is the first FDA-approved product for the treatment of FCS. The goal of treatment is to reduce the risk of acute pancreatitis and avoid long-term organ damage associated with it. There is no specific fasting triglyceride goal for this population of patients. Some literature suggests a goal <750 - 880 mg/dL is thought to reduce the risk of acute pancreatitis, but there is no consensus on this threshold.
- III. Olezarsen (Tryngolza) is indicated as an adjunct to diet to reduce triglycerides in adults with familial chylomicronemia syndrome (FCS). The pivotal trial that evaluated the safety and efficacy of olezarsen (Tryngolza) required participants to be 18 years of age or older. Safety and efficacy has not been established in pediatric patients.
- IV. Given the rarity and complexity of FCS, diagnosis and management should be directed by a specialist such as a cardiologist, endocrinologist, or provider that specializes in the treatment of lipid disorders.
- V. The study population in the Balance study, the pivotal clinical trial that evaluated the safety and efficacy of olezarsen (Tryngolza), were diagnosed with familial chylomicronemia syndrome. Diagnosis was confirmed with documentation of biallelic pathogenic variants in FCS-causing genes (e.g., LPL, GP1HBP1, APOA5, APOC2, or LMF1). Additionally, study participants were required to have fasting triglyceride levels ≥ 880 mg/dL and a history of pancreatitis (including episodes of acute pancreatitis). There have been US-based studies conducted to estimate the prevalence of FCS and most of those studies utilized a fasting triglyceride level of at least 880 mg/dL as one of the requirements for diagnosis. This population is at higher risk of experiencing acute pancreatitis compared to other populations with elevated fasting triglyceride levels.

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- VI. Although traditional lipid-lowering medications (e.g., statin, omega-3 fatty acid, fibrate, etc.) are normally ineffective in this population of patients, some triglyceride lowering may be exhibited depending on the patient. Traditional lipid-lowering medications are deemed ineffective if they do not lower triglyceride levels by at least 20%.
- VII. There are no established formal treatment guidelines for the management of FCS. Current standard of care involves lifestyle modifications such as implementing a low-fat diet (e.g., less than 20 g of fat intake daily) and avoiding alcohol consumption and medications known to increase triglyceride levels (e.g., thiazide diuretics, beta-blockers, second-generation antipsychotics, corticosteroids, exogenous estrogen, etc.).

Investigational or Not Medically Necessary Uses

- I. Olezarsen (Tryngolza) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Hypertriglyceridemia
 - i. Olezarsen (Tryngolza) is currently under investigation for the treatment of severe hypertriglyceridemia, and hypertriglyceridemia with atherosclerotic cardiovascular disease. There are multiple trials recruiting, currently active or completed with results yet to be posted. Requests for this indication are considered experimental and investigational at this time.

References

1. Tryngolza. Package insert. Ionis Pharmaceuticals, Inc.; December 2024
2. Tryngolza Product Dossier. Ionis Pharmaceuticals, Inc. January 2025.
3. Stroes ESG, Alexander VJ, Karwatowska-Prokopczuk E, et al. Olezarsen, Acute Pancreatitis, and Familial Chylomicronemia Syndrome. *N Engl J Med.* 2024;390(19):1781-1792. doi:10.1056/NEJMoa2400201
4. Virani SS, Morris PB, Agarwala A, et al. 2021 ACC Expert Consensus Decision Pathway on the Management of ASCVD Risk Reduction in Patients With Persistent Hypertriglyceridemia: A Report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol.* 2021;78(9):960-993. doi:10.1016/j.jacc.2021.06.011
5. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2019;73: e285–e350.

Related Policies

Currently there are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
Added gastroenterologist to required specialist prescriber and added criteria to allow confirmation of FCS via NAFCS score ≥ 45 . Updated supporting evidence.	10/2025
Policy created	05/2024

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP143

Description

Omacetaxine mepesuccinate (Synribo) is a reversible protein synthesis inhibitor which binds to the A-site cleft of the ribosomal subunit to interfere with chain elongation and inhibit protein synthesis. It acts independently of BCR-ABL1 kinase-binding activity, and has demonstrated activity against tyrosine kinase inhibitor-resistant BCR-ABL mutations.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
omacetaxine mepesuccinate (Synribo)	3.5 mg vial	Chronic or accelerated phase CML	Initial: 28 vials/28 days Maintenance: 14 vials/28 days

Initial Evaluation

- I. Omacetaxine mepesuccinate (Synribo) may be considered medically necessary when the following criteria below are met:
 - A. Medication is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
 - B. Medication will not be used in combination with other oncologic medications (i.e., will be used as monotherapy); **AND**
 - C. A diagnosis of **chronic myelogenous leukemia (CML)** when the following are met:
 1. CML is in chronic or accelerated phase; **AND**
 2. Member has a complete blood count preformed routinely during treatment; **AND**
 3. Treatment with at least TWO of the below tyrosine kinase inhibitors (TKI) has been ineffective, contraindicated, or not tolerated:
 - i. imatinib (Gleevec)
 - ii. bosutinib (Bosulif)
 - iii. nilotinib (Tasigna)
 - iv. dasatinib (Sprycel)
- II. Omacetaxine mepesuccinate (Synribo) 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. Medication is prescribed by, or in consultation with, an oncologist or hematologist; **AND**
- IV. Medication will not be used in combination with other oncologic medications (i.e., will be used as monotherapy); **AND**
- V. Clinical documentation of response to treatment, such as stabilization of disease or decrease in tumor size or spread is provided.

Supporting Evidence

- I. Omacetaxine mepesuccinate (Synribo) is indicated for the treatment of chronic or accelerated phase CML in patients resistant and/or intolerant to at least two tyrosine kinase inhibitors.
- II. Myelosuppression with Grade 3/4 neutropenia, thrombocytopenia, and anemia commonly occur; generally reversible, although may require treatment delay and/or a reduction in the number of treatment days with future cycles. Myelosuppression may rarely be fatal. Blood counts should be monitored in induction and maintenance cycles.
- III. Non-hematologic toxicities include Grade 3 or 4 hyperglycemia. Avoid use of omacetaxine mepesuccinate (Synribo) in the setting of poorly controlled diabetes.
- IV. Within the pivotal trial, disease progression was defined as reduction of cells expressing Philadelphia chromosome mutation, normalization of white blood cells, or until patient is no longer achieving clinical treatment benefit.
- V. Dosing with omacetaxine mepesuccinate (Synribo) in the initial phase is 1.25 mg/m² subcutaneously twice daily for 14 consecutive days every 28 days, over a 28-day cycle. This cycle is repeated at this dosing every 28 days until patients achieve a hematologic response. Following hematologic response, the maintenance dosing regimen is initiated, which is 1.25 mg/m² subcutaneously twice daily for 7 consecutive days every 28 days, over a 28-day cycle.

Investigational or Not Medically Necessary Uses

- I. There is limited to no evidence to support the use of omacetaxine mepesuccinate (Synribo) in any other condition.

References

1. Synribo [Prescribing Information]. North Wales, PA: Teva Pharmaceuticals USA Inc; November 2019.
2. Nicolini FE, Lipton JH, Kantarjian H, et al. Subcutaneous omacetaxine mepesuccinate in patients with chronic phase (CP) or accelerated phase (AP) chronic myeloid leukemia (CML) resistant/intolerant to two or three approved tyrosine-kinase inhibitors (TKIs) [abstract]. J Clin Oncol. 2012;30(suppl):abstract 6513.
3. Cortes J, Digumarti R, Parikh PM, et al. Phase 2 study of subcutaneous omacetaxine mepesuccinate for chronic-phase chronic myeloid leukemia patients resistant to or intolerant of tyrosine kinase inhibitors. Am J Hematol. 2013;88(5):350-4.
4. NCCN Clinical Practice Guideline in Oncology: Chronic Myeloid Leukemia. Version 2.2020. National Comprehensive Cancer Network. Available at https://www.nccn.org/professionals/physician_gls/PDF/cml.pdf. Updated September 25, 2019.

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Policy Implementation/Update:

Date Created	February 2013
Date Effective	February 2013
Last Updated	December 2019
Last Reviewed	12/2019

Action and Summary of Changes	Date
Prior authorization criteria transitioned to policy format. Extend approval duration to six months for initial approvals and 12 months for renewals. Required agent be used as monotherapy and not in combination with other oncologic medications.	12/2019

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP175

Description

Omalizumab (Xolair) is a subcutaneously administered monoclonal antibody that binds to IgE causing the IgE receptors to downregulate and limit the degree of release of the mediators of allergic response.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Provider Administered Agents*, **			
Product name	Indication*	Dosage form	Quantity limit
omalizumab (Xolair)	Chronic idiopathic urticaria/chronic spontaneous urticaria (CIU/CSU)	150 mg*	2 vials/28 days (1.2ml/28 days)
		150 mg/1 mL prefilled syringe/autoinjector	1/28 (1ml/28 days)
		300 mg/2 mL prefilled syringe/autoinjector	1/28 (2ml/28 days)
	Allergic asthma**	150 mg vial*	2 vials/28 days (1.2ml/28 days)
		75 mg/0.5 mL prefilled syringe/autoinjector	2/28 (1ml/28 days)
		150 mg/1 mL prefilled syringe/autoinjector	2/28 (2ml/28 days)
		300 mg/2 mL prefilled syringe/autoinjector	2/28 (4ml/28 days)
	Chronic rhinosinusitis with nasal polyposis (CRSwNP)**	150 mg vial*	8 vials/28 days (9.6ml/28 days)
		75 mg/0.5 mL prefilled syringe/autoinjector	2/28 (1ml/28 days)
		150 mg/1 mL prefilled syringe/autoinjector	2/28 (2ml/28 days)
		300 mg/2 mL prefilled syringe/autoinjector	4/28 (8ml/28 days)
	IgE-mediated Food Allergy	150 mg vial*	8 vials/28 days (9.6ml/28 days)
		75 mg/0.5 mL prefilled syringe/autoinjector	2/28 (1ml/28 days)
		150 mg/1 mL prefilled syringe/autoinjector	2/28 (2ml/28 days)
		300 mg/2 mL prefilled syringe/autoinjector	4/28 (8ml/28 days)

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	Systemic mastocytosis	150 mg/1.2mL vial*	2 vials/28 days (1.2 ml/28 days)
		150 mg/1 mL prefilled syringe/autoinjector	1/28 (1ml/28 days)
		300 mg/2 mL prefilled syringe/autoinjector	1/28 (2ml/28 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.

**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/>

***Quantity limit can vary by IgE level and body weight. Higher quantities may be appropriate or allowed in specific scenarios depending on IgE and weight. Reviewing clinician should refer to the dosing listed in Appendix at the end of this policy.

Initial Evaluation

- I. **Omalizumab (Xolair)** may be considered medically necessary when the following criteria below are met:
 - A. Medication is prescribed by, or in consultation with, a dermatologist or a physician specializing in allergy, pulmonology, immunology, or ENT (ear, nose, throat); **AND**
 - B. Must not be used in combination with another monoclonal antibody (e.g., benralizumab, dupilumab, mepolizumab, reslizumab, ensifentrine, etc.); **AND**
 - C. A diagnosis of one of the following:
 1. **Moderate to severe persistent allergic asthma; AND**
 - i. Member is six years of age or older; **AND**
 - ii. Member has a positive skin test or in vitro reactivity to a perennial aeroallergen; **AND**
 - iii. Member must weigh between 20 kg (44 lbs.) and 150 kg (330 lbs.); **AND**
 - iv. Member has a serum total IgE level, measured before the start of treatment, of either:
 - a. ≥ 30 IU/mL and ≤ 700 IU/mL in members age ≥ 12 years; **OR**
 - b. ≥ 30 IU/mL and ≤ 1300 IU/mL in members age 6 to <12 years; **AND**
 - v. Member has **MODERATE** asthma as defined by one of the following:
 - a. Daily symptoms
 - b. Nighttime awakenings $> 1x/week$ but not nightly
 - c. SABA (e.g. albuterol, levalbuterol) use for symptom control occurs daily
 - d. Some limitation to normal activities
 - e. Lung function (percent predicted FEV1) $>60\%$, but $<80\%$
 - f. Exacerbations requiring oral systemic corticosteroids are generally more frequent and intense relative to mild asthma; **OR**
 - vi. Member has **SEVERE** asthma as defined by one of the following:
 - a. Symptoms throughout the day
 - b. Nighttime awakenings, often $7x/week$
 - c. SABA (e.g. albuterol, levalbuterol) use for symptom control occurs several times per day
 - d. Extremely limited normal activities

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- e. Lung function (percent predicted FEV1) <60%
 - f. Exacerbations requiring oral systemic corticosteroids are generally more frequent and intense relative to moderate asthma; **AND**
- vii. Member is currently being treated with:
 - a. A medium- to high-dose, or maximally tolerated inhaled corticosteroid (ICS) [e.g., budesonide, fluticasone, mometasone]; **AND**
 - i. 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}, leukotriene receptor antagonist [e.g., Singular], or theophylline); **OR**
 - b. A maximally tolerated ICS/LABA combination product (e.g., Advair, Airduo, Breo, Dulera, Symbicort); **OR**
- 2. **Chronic idiopathic urticaria/chronic spontaneous urticaria (CIU/CSU); AND**
 - i. Member is 12 years of age or older; **AND**
 - ii. Underlying cause of the member's condition is NOT considered to be any other allergic condition(s) or other form(s) of urticaria; **AND**
 - iii. Member is avoiding triggers (e.g., NSAIDs, etc.); **AND**
 - iv. Member had an inadequate response to a minimum (1) month trial on previous therapy of a second-generation H1-antihistamine product*; **AND**
 - v. Member had an inadequate response to a minimum (1) month trial on previous therapy of at least one of the following:
 - 1. Updosing/dose advancement (up to 4-fold) of a second generation H1-antihistamine*
 - 2. Add-on therapy with a leukotriene antagonist (e.g., montelukast, zafirlukast, etc.)
 - 3. Add-on therapy with another H1-antihistamine*
 - 4. Add-on therapy with a H2-antagonist (e.g. ranitidine, etc.)
 - 5. Add-on therapy with cyclosporine; **AND**
- 3. **Systemic mastocytosis; AND**
 - i. Member is 18 years of age or older; **AND**
 - ii. Used for the prevention of one of the following:
 - a. Chronic mast-cell-mediator-related cardiovascular (e.g., pre-syncope, tachycardia, etc.) or pulmonary (e.g., wheezing, throat-swelling, etc.) symptoms insufficiently controlled by conventional therapy (e.g., H1 or H2 blockers or corticosteroids); **OR**
 - b. Unprovoked anaphylaxis; **OR**
 - c. Hymenoptera or food-induced anaphylaxis in members with a negative test for specific IgE antibodies or a negative skin test; **OR**
 - iii. Used to improve tolerance while on immunotherapy (i.e., venom immunotherapy [VIT]); **OR**
- 4. **Chronic rhinosinusitis with nasal polypsis (CRSwNP); AND**
 - i. Member is 18 years of age or older; **AND**
 - ii. Member must weigh between 30 kg (66 lbs.) and 150 kg (330 lbs.); **AND**

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- iii. Member has a serum total IgE level ≥ 30 IU/mL and ≤ 1500 IU/mL measured before the start of treatment; **AND**
- iv. Provider attests that the member has ALL of the following:
 - a. Diagnosis of bilateral sinonasal polyposis as evidenced by an endoscopy or computed tomography (CT); **AND**
 - b. Member has impaired Health-Related Quality of Life due to ongoing nasal congestion, blockage, or obstruction with moderate to severe symptom severity; **AND**
 - c. Member has at least one of the following symptoms:
 - i. Nasal discharge
 - ii. Facial pain or pressure
 - iii. Reduction or loss of smell; **AND**
- v. Provider attestation or clinical documentation that member has current persistent symptomatic nasal polyps despite maximal treatment with an intranasal corticosteroid, unless ineffective, not tolerated, or contraindicated; **AND**
- vi. Background intranasal corticosteroid will be continued with the use of omalizumab (Xolair), unless contraindicated; **OR**

5. Food Allergies; AND

- i. Member is one year of age or older; **AND**
- ii. Member has a serum total IgE level ≥ 30 IU/mL and ≤ 1850 IU/mL measured before the start of treatment; **AND**
- iii. Member weight is provided; **AND**
- iv. Omalizumab (Xolair) not be used in combination with oral immunotherapy (e.g., peanut allergen powder-dnfp (Palforzia) or other peanut desensitization therapy); **AND**
- v. Member has a diagnosis of IgE-mediated food allergy, as demonstrated by:
 - a. At least one IgE-mediated food allergy (i.e., peanut, milk, egg, wheat, or tree nuts, etc); **AND**
 - b. Confirmation of food allergy by at least one of the following:
 - i. Positive skin prick test or serologic evidence of IgE-mediated antibody to a potent extract of the allergen; **OR**
 - ii. Reacted to an oral food challenge; **AND**
 - c. Provider attestation of all of the following:
 - i. Member has a history of Type 1 reaction (e.g., hives, rash, stomach cramps, vomiting, etc.) or anaphylaxis from ingestion of one or more food allergens; **AND**
 - ii. Member will continue to practice food avoidance to reduce risk of anaphylaxis while on omalizumab (Xolair); **AND**
 - iii. Member has an active prescription for epinephrine.

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

A. Management of Immune Checkpoint Inhibitor related toxicity

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- B. Eosinophilic esophagitis
- C. Interstitial cystitis
- D. Painful bladder syndrome
- E. Eosinophilic bronchitis
- F. Multi-food oral immunotherapy
- G. Bullous pemphigoid
- H. Solar urticaria
- I. Cholinergic urticaria
- J. Seasonal allergic rhinitis
- K. Emergency treatment of any allergic reaction, including anaphylaxis
- L. Non-IgE-mediated food allergy, other food reactions (e.g., celiac 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. Must not be used in combination with another monoclonal antibody (e.g., benralizumab, dupilumab, mepolizumab, reslizumab, ensifentrine, etc.); **AND**
- IV. A diagnosis of one of the following:
 - i. **Moderate to severe persistent allergic asthma; AND**
 - 1. Member must weigh between 20 kg (44 lbs.) and 150 kg (330 lbs.); **AND**
 - 2. Member has exhibited improvement or stability of disease symptoms (e.g., reduced asthma exacerbations, FEV1, reduced systemic corticosteroid requirements, reduced hospitalizations); **OR**
 - ii. **Chronic idiopathic urticaria/chronic spontaneous urticaria (CIU/CSU); AND**
 - 1. Member has exhibited improvement or stability of disease symptoms from baseline (e.g. decreased itch severity, decreased number of hives or decreased size of hives, etc.); **OR**
 - iii. **Systemic mastocytosis; AND**
 - 1. Member has exhibited improvement or stability of disease symptoms compared to baseline (e.g., decreased frequency of exacerbations); **OR**
 - iv. **Chronic rhinosinusitis with nasal polyposis (CRSwNP); AND**
 - 1. Member must weigh between 30 kg (66 lbs.) and 150 kg (330 lbs.); **AND**
 - 2. Member has exhibited improvement or stability of disease symptoms (e.g., improvement in nasal congestion/obstruction severity, reduction in nasal polyps); **AND**
 - 3. Background intranasal corticosteroid (e.g., beclomethasone [Qnasl], budesonide [Rhinocort], ciclesonide [Omnaris; Zetonna], flunisolide, fluticasone [Flonase], mometasone [Nasonex], triamcinolone [Nasacort]) will be continued with the use of omalizumab (Xolair), unless contraindicated.
- 4. **IgE-mediated Food Allergies; AND**
 - i. Provider attestation that omalizumab (Xolair) continues to reduce allergic reactions to more than one type of food after accidental exposure and treatment provides clinical benefit to the member; **AND**

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- ii. Treatment will not be used in combination with oral immunotherapy (e.g., peanut allergen powder-dnfp (Palforzia) or other peanut desensitization therapy); **AND**
- iii. Member continues to practice food avoidance to reduce risk of anaphylaxis; **AND**
- iv. Member has an active prescription for epinephrine

Supporting Evidence

- I. There is a lack of evidence supporting treatment with dual use of biologic therapies and a potential for increased risk of side effects.
- II. Omalizumab (Xolair) is FDA approved for moderate to severe persistent asthma in patients 6 years of age and older with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids (ICS), as add-on maintenance treatment for patients 18 years of age with chronic rhinosinusitis with nasal polyps (CRSwNP), as chronic spontaneous urticaria in patients 12 years of age and older who remain symptomatic despite H1 antihistamine treatment, and for immunoglobulin E (IgE)-mediated food allergy in adult and pediatric patients 1 year of age and older for the reduction of allergic reactions (Type I) that may occur with accidental exposure to one or more foods.
 - Omalizumab (Xolair) is not FDA approved for use in the setting of systemic mastocytosis; however, it is compendia recommended.
- III. Omalizumab (Xolair) prefilled syringes and autoinjectors have been FDA approved for self-administration for the treatment of asthma in patients 6 years and older, chronic spontaneous urticaria (CSU) in patients 12 years and older, nasal polyps in patients aged 18 years and older, and IgE-mediated food allergies in patients aged 1 year and older. According to the package insert, therapy should be initiated in a healthcare setting. Once therapy has been safely established, the healthcare provider may determine whether self-administration of omalizumab (Xolair) is appropriate, based on careful assessment of risk for anaphylaxis and risk reduction strategies. Patient-specific factors considered when selecting patients for self-administration include the following criteria:
 - Patient should have no prior history of anaphylaxis, including to XOLAIR or other agents, such as latex, foods, drugs, biologics, etc.
 - Patient should receive at least 3 doses of XOLAIR under the guidance of a healthcare provider with no hypersensitivity reactions
 - Patient or caregiver is able to recognize symptoms of anaphylaxis
 - Patient or caregiver is able to treat anaphylaxis appropriately
 - Patient or caregiver is able to perform subcutaneous injections with XOLAIR prefilled syringe or autoinjector with proper technique according to the prescribed dosing regimen and Instructions for Use
- IV. Omalizumab (Xolair) autoinjectors at all doses are not intended for use in pediatric patients under 12 years of age.
- V. **Moderate to severe persistent allergic asthma**
 - For patients 12 years of age and older, omalizumab (Xolair) was studied in 3 randomized, double-blind, placebo-controlled, multicenter trials. The patients enrolled in these trials were 12 to 76 years of age, with moderate to severe

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persistent asthma for at least one year, and a positive skin test reaction to a perennial aeroallergen. All patients were required to have a baseline IgE level between 30 and 700 IU/mL and body weight ≤ 150 kg. Patients with IgE levels less than 30 IU/mL, greater than 700 IU/mL, or a weight greater than 150 kg have not been studied and efficacy has not been demonstrated in a randomized controlled clinical trial.

- i. Trials 1 and 2: All patients were symptomatic and were treated with ICS/SABA. The primary endpoint was mean number asthma exacerbations per patient during steroid stable phase versus steroid reduction phase in comparison to placebo. In the stable steroid phase, the mean number of exacerbations per patient was 0.2 in the active arm compared to 0.3 in the placebo arm, p-value=0.005 (Trial 1) and 0.1 in the active arm compared to 0.4 in the placebo arm, p-value<0.001 (Trial 2). In the steroid reduction phase, the mean number of exacerbations per patient was 0.2 in the active arm compared to 0.4 in the placebo arm, p-value=0.004 (Trial 1) and 0.2 in the active arm compared to 0.3 in the placebo arm, p-value<0.001 (Trial 2).
 - ii. Trial 3: Long-acting beta2-agonists were allowed. Patients received at least 1000 mcg/day fluticasone propionate and a subset also received oral corticosteroids (OCS). The primary endpoint was percentage of patients with at least 1 exacerbation during steroid stable phase versus steroid reduction phase in comparison to placebo. In the stable steroid phase, the treatment difference in percentage of patients with at least one exacerbation was 0.9 (95% CI -9.7, 13.7) in the ICS only arm compared to 9.8 (95% CI -10.5, 31.4) in the OCS/ICS arm. In the steroid reduction phase, the treatment difference in percentage of patients with at least one exacerbation was -4.4 (95% CI -17.6, 7.4) in the ICS only arm compared to -0.2 (95% CI -22.4, 20.1) in the OCS/ICS arm.
- For patients 6 to <12 years of age, omalizumab (Xolair) was studied in one double-blind, placebo controlled, multi-center trial. All patients were required to have a baseline IgE level between 30 and 1300 IU/mL and body weight between 20 to 150 kg. The primary endpoint was the rate of asthma exacerbations during the 24-week, fixed steroid treatment phase, which was 0.45 in the active arm compared to 0.64 in the placebo arm (RR 0.69, 95% CI 0.53, 0.9).
 - The Global Initiative for Asthma (GINA) 2020 update recommends the addition of respiratory biologics, with respect to their allergic biomarkers, after inadequate asthma control despite good adherence and inhaler technique on maximized Step 4 (medium dose ICS-LABA) or Step 5 (high dose ICS-LABA) therapy. Other controller options for Step 4 include high dose ICS-LABA or add-on tiotropium, or add-on LTRA. Other controller options for Step 5 include add-on anti-IL5, or add-on low dose OCS, though guidelines note to consider side effects.
 - Dose adjustments should be considered for drastic changes in body weight. Dosing should not be adjusted based off IgE levels unless therapy has been interrupted for greater than one year. A minimum of three to six months of treatment is suggested to reach maximum efficacy.

VI. **Chronic idiopathic urticaria/chronic spontaneous urticaria (CIU/CSU)**

- Omalizumab (Xolair) was studied in two placebo-controlled, multiple-dose clinical trials. Patients received omalizumab (Xolair) 75 mg, 150 mg, or 300 mg or placebo by subcutaneous injection every 4 weeks in addition to their baseline level of H1 antihistamine therapy for 24 or 12 weeks, followed by a 16-week washout observation period. Per the prescribing label, the 75-mg dose did not demonstrate consistent evidence of efficacy and is not approved for use in CIU. Clinical trials required a UAS7 score of greater than or equal to 16 with weekly reassessments to objectively measure treatment benefit. The primary endpoints were mean weekly itch severity score and weekly hive count.

	XOLAIR 75mg	XOLAIR 150mg	XOLAIR 300mg	Placebo
n	77	80	81	80
Weekly Itch Severity Score				
Mean Baseline Score (SD)	14.5 (3.6)	14.1 (3.8)	14.2 (3.3)	14.4 (3.5)
Mean Change Week 12 (SD)	-6.46 (6.14)	-6.66 (6.28)	-9.40 (5.73)	-3.63 (5.22)
Difference in LS means vs. placebo	-2.96	-2.95	-5.80	
95% CI for difference	-4.71, -1.21	-4.72, -1.18	-7.49, -4.10	-
Weekly Hive Count Score [†]				
Mean Baseline Score (SD)	17.2 (4.2)	16.2 (4.6)	17.1 (3.8)	16.7 (4.4)
Mean Change Week 12 (SD)	-7.36 (7.52)	-7.78 (7.08)	-11.35 (7.25)	-4.37 (6.60)
Difference in LS means vs. placebo	-2.75	-3.44	-6.93	
95% CI for difference	-4.95, -0.54	-5.57, -1.32	-9.10, -4.76	-

- Per the EAACI/GA²LEN/EDF/WAO guidelines for the definition, classification, diagnosis, and management of urticaria first line treatment for CSU is a 2nd generation H1-antihistamine. If there is inadequate control or response, then it is recommended to increase the 2nd generation H1-antihistamine dose up to 4x the standard dose. If there is no adequate response to the high dose 2nd generation H1-antihistamine after 2-4 weeks, then adding omalizumab (Xolair) 300 mg every 4 weeks is recommended. The guidelines also state that H2-antihistamines (e.g. ranitidine) and leukotriene receptor antagonist (e.g. montelukast) may be alternative treatment options for certain clinical scenarios.
- Per the JTFPP guidelines on the diagnosis and management of acute and chronic spontaneous urticaria it is recommended that first line treatment to be with a 2nd generation H1-antihistamine and the avoidance of triggers (e.g. NSAIDs). If symptoms are still uncontrolled then second line treatment can be one or more of the following: dose advancement of 2nd generation H1-antihistamine, add another second-generation antihistamine, add a H2-antihistamine, add a leukotriene receptor antagonist, or add a 1st generation antihistamine to be taken at bedtime.
- Per clinical trials of patients with CIU taking Omalizumab (Xolair), 36% of patients treated with 300 mg reported no itch or hives at week 12 compared to 15% treated with 150 mg, 12% with 75mg, and 9% with placebo.
- There is limited data regarding the continuation of Omalizumab (Xolair) and the need for dose reductions. Preliminary studies discuss the potential for dose reductions or increased dosing intervals, although there is currently no consensus on the best method.

VII. Systemic mastocytosis

- Omalizumab (Xolair) is recommended per NCCN guidelines for Systemic Mastocytosis for the treatment of mast-cell-mediator-related cardiovascular or pulmonary symptoms after prior trial of an H1 blocker, H2 blocker, and corticosteroids. Use of omalizumab (Xolair) for the management of Systemic Mastocytosis is supported by case studies and prospective reviews, though no clinical trials have been completed. Omalizumab (Xolair) has been found to prevent mast-cell-mediator-related cardiovascular or pulmonary symptoms despite use of conventional therapies and has been shown to improve tolerance while on immunotherapy.

VIII. Chronic rhinosinusitis with nasal polyposis (CRSwNP)

- Omalizumab (Xolair) was studied as an add-on therapy with background intranasal corticosteroid in adult patients with CRSwNP with inadequate response to intranasal corticosteroids. Omalizumab (Xolair) was evaluated in two identical phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter trials. Trials enrolled patients aged 18 through 75 years with persistent bilateral nasal polyps, nasal congestion, impaired HRQoL, and weight 30-150 kg and serum IgE level 30- 1500 IU/mL. The primary endpoints were change from baseline to week 24 in endoscopic nasal polyp score (NPS) and mean daily nasal congestion score (NCS). Key secondary endpoints were change from baseline at week 24 in Sino-Nasal Outcome Test-22 (SNOT-22) score, University of Pennsylvania Smell Identification Test (UPSIT) score, and Asthma Quality of Life Questionnaire (AQLQ).

	POLYP 1			POLYP 2		
	PBO N=66	OMA N=72	Treatment Difference (95% CI), p-value	PBO N=65	OMA N=62	Treatment Difference (95% CI), p-value
Primary Endpoint						
NPS (range, 0-8)	0.06 (0.16)	-1.08 (0.16)	-1.14 (-1.59 to - 0.69) p<0.0001	-0.31 (0.16)	-0.9 (0.19)	-0.59 (-1.05 to 0.12) p<0.14
NCS (range, 0-3)	-0.35 (0.11)	-0.89 (0.1)	-0.55 (-0.84 to - 0.25) p<0.0004	-0.20 (0.11)	-0.70 (0.11)	-0.50 (-0.80 to - 0.19) p<0.0017
Secondary Endpoint						
SNOT-22 score (range, 0-110)	-8.58 (2.08)	-24.70 (2.01)	-16.12 (-21.86 to - -10.38) p<0.0001	-6.55 (2.19)	-21.59 (2.25)	-15.04 (-21.26 to - 8.82) p<0.0001
UPSIT score (range, 0-40)	0.63 (0.90)	4.44 (0.84)	3.81 (1.38-6.24) p<0.0024	0.44 (0.81)	4.31 (0.83)	3.86 (1.57-6.15) p<0.0011
AQLQ score, OR of MCID (≥0.5-point improvement)	OR 3.71 (95% CI 1-13.71, p=0.0492)			OR 4.04 (95% CI 1.07-15.25, p=0.0396)		

MCID: minimal clinically important difference

- The American Academy of Allergy, Asthma, and Immunology (AAAAI), American College of Allergy, Asthma, and Immunology (ACAAI), and Joint Council of Allergy, Asthma, and Immunology (JCAAI) 2014 guidelines recommend short-term treatment with oral steroids in patients with CRSwNP “because it decreases nasal polyp size and symptoms”. Additionally, guidelines recommend both intranasal corticosteroids and omalizumab for treatment of CRSwNP.

IX. IgE-mediated Food Allergies

- Omalizumab (Xolair) is the first FDA-approved medication to reduce the health impact of allergic reactions to more than one type of food after accidental exposure. Goals of treatment include increasing tolerance to small amounts of food allergens and reducing the chances of having a severe anaphylactic reaction upon accidental ingestion. There is currently no cure for food allergy; management requires the patient to strictly avoid any exposure to known allergens, along with prompt administration of epinephrine to treat anaphylaxis if accidental exposures occur. Therefore, the use of omalizumab (Xolair) is reserved for members with medical history of severe food allergy reactions that cannot be managed despite food avoidance to control allergic symptoms and conventional therapies such as antihistamines (e.g., reaction causes anaphylaxis, requires epinephrine use, allergy that can be triggered by smell).
- Coverage requires a confirmed food allergy diagnosis consisting of a clinical history of allergy along with confirmatory values with a positive skin prick test and elevated serum IgE levels or food challenge, as per guideline recommendations.
- The efficacy and safety of omalizumab (Xolair) was evaluated in 168 pediatric patients in a phase 3, randomized, placebo-controlled trial (OUTMATCH). The study enrolled patients 1 - 55 years of age who were allergic to peanut and at least two other foods, including milk, egg, wheat, cashew, hazelnut, or walnut. Patients were randomized 2:1 to receive Xolair or placebo SC based on serum total IgE level and body weight, for 16 to 20 weeks. The study excluded patients with severe anaphylaxis and high baseline IgE levels (>1500mg). The primary endpoint evaluated the percentage of patients who were able to consume a single dose of ≥ 600 mg of peanut protein (~2.5 peanuts or $\frac{1}{2}$ teaspoon of regular peanut butter) without moderate to severe allergic symptoms. Omalizumab (Xolair) treatment led to a statistically higher response rate compared to placebo (68% omalizumab vs. 5% placebo; treatment difference, 63% [95% CI, 50% to 73%]). However, 17% of subjects receiving omalizumab (Xolair) had no significant change in the amount of peanut protein tolerated (could not tolerate 100 mg or more of peanut protein). The incidence of adverse events was similar between groups and no new safety signals were identified.
- Omalizumab (Xolair) does not modulate any food response and patients must still practice food avoidance. There is unknown clinical significance and meaningfulness of improving tolerance of a single dose of 600 mg peanut protein. Furthermore, tolerance of 600 mg of peanut protein did not result in improvements in quality of life and reductions in reactions to accidental exposure to peanuts in the clinical trial.
- Restricted to treating peanut allergy, peanut allergen powder-dnfp (Palforzia) is an oral immunotherapy product approved in patients 4–17 years of age for the mitigation of allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut. Safety and efficacy of combination treatment has not been evaluated and is therefore considered experimental and investigational. Furthermore, patients taking Palforzia were excluded from participating in the clinical trial evaluating omalizumab (Xolair).

Investigational or Not Medically Necessary Uses

- I. Omalizumab (Xolair) has not been adequately studied for the following conditions and does not have established safety and efficacy in these populations:
 - A. Management of Immune Checkpoint Inhibitor related toxicity
 - i. Though use is supported by NCCN guidelines for Management of Immunotherapy-related toxicities, there are no clinical trials demonstrating clinical efficacy or safety of the use of omalizumab (Xolair) in the treatment of Immune Checkpoint Inhibitor related toxicity.
 - B. Emergency treatment of any allergic reaction, including anaphylaxis
 - C. Non-IgE-mediated food allergy, other food reactions (e.g., celiac disease)
 - i. Non-IgE mediated food allergies present as more subacute and/or chronic symptoms that are typically isolated to the GI tract and/or skin. Of note, celiac disease is caused by a non-IgE-mediated immune reaction to a food protein (gluten) and having a diagnosis alone is not considered a food allergy.
 - D. Ongoing clinical trials for the following conditions without outcomes demonstrating efficacy of treatment:
 - i. Eosinophilic esophagitis
 - ii. Interstitial cystitis
 - iii. Painful bladder syndrome
 - iv. Eosinophilic bronchitis
 - v. Multi-food oral immunotherapy
 - vi. Bullous pemphigoid
 - vii. Solar urticaria
 - viii. Cholinergic urticaria
 - ix. Seasonal allergic rhinitis

Appendix

I. Table 1: Indication and dosing

Indication	Dose
Allergic Asthma	75 to 375 mg administered subcutaneously every 2 or 4 weeks. Determine dose (mg) and dosing frequency by serum total IgE level (IU/mL), measured before the start of treatment, and body weight (kg). See tables below.
Chronic idiopathic urticaria	150 or 300 mg administered subcutaneously every 4 weeks. Dosing is not dependent on serum IgE (free or total) level or body weight.
Chronic rhinosinusitis with nasal polyposis	75 to 600 mg SC administered subcutaneously every 2 or 4 weeks. Determine dose (mg) and dosing frequency by serum total IgE level (IU/mL), measured before the start of treatment, and body weight (kg). See tables below.
IgE-mediated Food Allergies	75 to 600 mg SC administered subcutaneously every 2 or 4 weeks. Determine dose (mg) and dosing frequency by serum total IgE level (IU/mL), measured before the start of treatment, and body weight (kg). See tables below.
All other indications	150 or 300 mg administered subcutaneously by a health care provider every 4 weeks. Dosing is not dependent on serum IgE (free or total) level or body weight.

II. Table 1: Weight based dosing every 2 or 4 weeks in members ≥ 12 years of age and older with Asthma

Omalizumab administered every 2 or 4 weeks (mg) in members ≥ 12 years with asthma					
Pre-treatment serum IgE (IU/mL)	Dosing Frequency	Body weight (kg)			
		30 to 60	> 60 to 70	> 70 to 90	> 90 to 150
≥ 30 to 100	Every 4 weeks	150	150	150	300
> 100 to 200		300	300	300	225
> 200 to 300		300	225	225	300
>300 to 400	Every 2 weeks	225	225	300	Insufficient Data to recommend a dose
>400 to 500		300	300	375	
>500 to 600		300	375		
>600 to 700		375			

III. Table 2: Weight based dosing every 2 or 4 weeks for in members who begin Xolair between the ages of 6 to <12 years for Asthma

Omalizumab Doses Administered Every 2 or 4 Weeks (mg) for Pediatric Members with Asthma Who Begin Xolair Between the Ages of 6 to <12 Years											
Pre-treatment IgE (IU/mL)	Dosing Freq. (weeks)	Body Weight (kg)									
		20-25	>25-30	>30-40	>40-50	>50-60	>60-70	>70-80	>80-90	>90-125	>125-150
30-100	Every 4 weeks	75	75	75	150	150	150	150	150	300	300
>100-200		150	150	150	300	300	300	300	300	225	300
>200-300		150	150	225	300	300	225	225	225	300	375
>300-400		225	225	300	225	225	225	300	300	Insufficient data to recommend a dose	
>400-500		225	300	225	225	300	300	375	375		
>500-600		300	300	225	300	300	375	Insufficient data to recommend a dose			
>600-700		300	225	225	300	375	Insufficient data to recommend a dose				
>700-900	Every 2 weeks	225	225	300	375	Insufficient data to recommend a dose					
>900-1100		225	300	375							
>1100-1200		300	300								
>1200-1300		300	375								

IV. Table 3. Weight based dosing every 2 or 4 weeks for adults with CRSwNP

Omalizumab Doses Administered Every 2 or 4 Weeks (mg) for adults with CRSwNP										
Pretreatment Serum IgE (IU/mL)	Dosing Freq.	Body Weight								
		>30-40kg	>40-50kg	>50-60kg	>60-70kg	>70-80kg	>80-90kg	>90-125kg	> 125-150kg	
Dose (mg)										
30 - 100	Every 4 weeks	75	150	150	150	150	150	300	300	
>100 -200		150	300	300	300	300	300	450	600	
>200 - 300		225	300	300	450	450	450	600	375	
>300 - 400		300	450	450	450	600	600	450	525	
>400 - 500		450	450	600	600	375	375	525	600	
>500 - 600		450	600	600	375	450	450	600		
>600 - 700		450	600	375	450	450	525			
>700 - 800	Every 2 weeks	300	375	450	450	525	600			
>800 - 900		300	375	450	525	600				
>900 - 1000		375	450	525	600					
>1000 - 1100		375	450	600						
>1100 - 1200		450	525	600	Insufficient Data to Recommend a Dose					
>1200 - 1300		450	525							
>1300 - 1500		525	600							

Insufficient Data to Recommend a Dose

V. Table 4: Weight based dosing for adult and pediatric members with IgE-mediated Food Allergies

Omalizumab Doses Administered Every 2 or 4 Weeks (mg) for adult and pediatric members with IgE-Mediated Food Allergy														
Pretreatment Serum IgE (IU/mL)	Dosing Freq.	Body Weight (kg)												
		≥10-12	>12-15	>15-20	>20-25	>25-30	>30-40	>40-50	>50-60	>60-70	>70-80	>80-90	>90-125	> 125-150
Dose (mg)														
30 - 100	Every 4 weeks	75	75	75	75	75	75	150	150	150	150	150	300	300
>100 -200		75	75	75	150	150	150	300	300	300	300	300	450	600
>200 - 300		75	75	150	150	150	225	300	300	450	450	450	600	375
>300 - 400		150	150	150	225	225	300	450	450	450	600	600	450	525
>400 - 500		150	150	225	225	300	450	450	600	600	375	375	525	600
>500 - 600		150	150	225	300	300	450	600	600	375	450	450	600	
>600 - 700		150	150	225	300	225	450	600	375	450	450	525		
>700 - 800	Every 2 weeks	150	150	150	225	225	300	375	450	450	525	600		
>800 - 900		150	150	150	225	225	300	375	450	525	600			
>900 - 1000		150	150	225	225	300	375	450	525	600				
>1000 - 1100		150	150	225	225	300	375	450	600					

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>1100 - 1200		150	150	225	300	300	450	525	600	Insufficient Data to Recommend a Dose
>1200 - 1300		150	225	225	300	375	450	525		
>1300 - 1500		150	225	300	300	375	525	600		
>1500 - 1850			225	300	375	450	600			

VI. Abbreviated list of H1 antihistamine products:

*H1 Antihistamine Products (not all inclusive)	
- fexofenadine - loratadine - desloratadine - cetirizine - levocetirizine - clemastine - diphenhydramine	- chlorpheniramine - hydroxyzine - cypheptadine - brompheniramine - triprolidine - dexchlorpheniramine - carbinoxamine

References

1. Xolair [package insert]. South San Francisco, CA; Genentech, Inc.; Updated February 2024. Accessed February 2024.
2. National Asthma Education and Prevention Program (NAEPP). Guidelines for the diagnosis and management of asthma. Expert Panel Report 3. Bethesda, MD: National Institutes of Health (NIH), National Heart, Lung, and Blood Institute (NHLBI); August 2007.
3. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2020 Update. Available from: <http://www.ginasthma.org>. Accessed February 2021.
4. Baiardini I, Braidò F, Bindslev-Jensen C, et al. Recommendations for assessing member-reported outcomes and health-related quality of life in members with urticaria: a GA(2)
5. National Comprehensive Cancer Network clinical practice guidelines, systemic mastocytosis. Version 1.2020. Updated May 21, 2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/mastocytosis.pdf. Accessed February 1, 2021.
6. Broesby-Olsen S1, Vestergaard H2, Mortz CG, et al. Omalizumab prevents anaphylaxis and improves symptoms in systemic mastocytosis: Efficacy and safety observations. *Allergy*. 2018 Jan;73(1):230-238. doi: 10.1111/all.13237. Epub 2017 Jul 27.
7. National Comprehensive Cancer Network clinical practice guidelines, management of immunotherapy-related toxicities. Version 1.2020. Updated December 16, 2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf. Accessed February 6, 2020.
8. Gevaert P, Omachi TA, Corren J et al. Efficacy and safety of omalizumab in nasal polyposis: 2 randomized phase 3 trials. *J Allergy Clin Immunol* 2020;146(3):595-605. Available at: <https://pubmed.ncbi.nlm.nih.gov/32524991/>. Accessed January 27, 2021.
9. Peters AT, Spector S, Hsu J, et al. Diagnosis and management of rhinosinusitis: a practice parameter Update. *Ann Allergy Asthma Immunol* 2014 (113):347-385. Available at: http://www.aaaai.org/Aaaai/media/MediaLibrary/PDF%20Documents/Practice%20and%20Parameters/2014-October_Rhinosinusitis_Update.pdf. Accessed January 27, 2021.
10. Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA2LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. *Allergy*. 2018;73(7):1393-1414.
11. UpToDate. Anti-IgE Therapy, Updated November 18, 2021. Accessed June 3, 2022.
12. Wood RA, Togias A, Sicherer SH, et al. Omalizumab for the Treatment of Multiple Food Allergies. *N Engl J Med*. 2024;390(10):889-899. doi:10.1056/NEJMoa2312382
13. Asthma and Allergy Foundation of America. The allergic or atopic march. June 2022. Accessed March 7, 2024. <https://aafa.org/allergies/prevent-allergies/allergic-march/>
14. Bright DM, et al. Food allergies: Diagnosis, treatment, and prevention. *Am Fam Physician*. 2023;108(2):159-165.
15. Sampson HA, et al. Food allergy: a practice parameter update-2014. *J Allergy Clin Immunol*. 2014;134(5):1016-25.e43. doi:10.1016/j.jaci.2014.05.013

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16. Santos AF, et al. EAACI guidelines on the diagnosis of IgE-mediated food allergy. *Allergy*. 2023;78(12):3057-3076. doi:10.1111/all.15902
17. NIAID-Sponsored Expert Panel, Boyce JA, Assa'ad A, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol*. 2010;126(6 Suppl):S1-S58. doi:10.1016/j.jaci.2010.10.007
18. Fleischer DM, et al. A consensus approach to the primary prevention of food allergy through nutrition: Guidance from the American Academy of Allergy, Asthma, and Immunology; American College of Allergy, Asthma, and Immunology; and the Canadian Society for Allergy and Clinical Immunology. *J Allergy Clin Immunol Pract*. 2021;9(1):22-43.e4. doi:10.1016/j.jaip.2020.11.002
19. Bernstein JA, Lang DM, Khan DA, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. *J Allergy Clin Immunol*. 2014;133(5):1270-1277. doi:10.1016/j.jaci.2014.02.036

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
	Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)
	Prurigo Nodularis
	Eosinophilic Esophagitis
	Chronic Obstructive Pulmonary Disease (COPD)
	Chronic Spontaneous Urticaria (CSU)
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)
tezepelumab (Tezspire®) Policy	Asthma (severe)
peanut allergen powder-dnfp (Palforzia™)	Peanut allergy

Policy Implementation/Update:

Action and Summary of Changes	Date
Removed documentation of objective clinical evaluation assessment from initial and renewal criteria in setting of CSU. Updated related policies.	07/2025
Removed oral steroid requirement for CRSwNP.	03/2025
Updated food allergy indication to include any food allergen.	06/2024
Updated policy to include IgE-mediated food allergies indication. Updated quantity limits table. Updated CSU to CIU given name change as adapted by clinical practice guidelines. Updated E/I to remove urticaria given Xolair, and added emergency treatment of any allergic reaction, including anaphylaxis and non-IgE-mediated food allergy, other food reactions (e.g., celiac disease). Updated appendix with dosing tables, supporting evidence, references. Added related policies.	03/2024
Updated quantity limit for CIU and supporting evidence (dose recommendation)	06/2022
Update to supporting evidence (self-administration of Xolair)	05/2021
Updated policy to include chronic rhinosinusitis with nasal polyposis (CRSwNP) indication. Updated policy to include route of administration under Description, PBO program under Quantity Limits. For Initial Evaluation: added medication is prescribed by, or in consultation with, a dermatologist or a physician specializing in allergy, pulmonology, immunology, or ENT (ear, nose, throat); asthma: removed moderate and severe asthma definition table in supporting evidence and built into criteria set, revised verbiage of previous combination therapy use and added “;OR a maximally tolerated ICS/LABA combination product”. For Renewal Evaluation: asthma: revised to updated renewal verbiage and consolidated list of clinical	03/2021

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improvement examples; CIU and systemic mastocytosis: revised to updated renewal verbiage. For supporting evidence: removed subjective verbiage and included more detailed information regarding each policy indication.	
Convert to Policy format. Removed Management of Immune Checkpoint Inhibitor related toxicity criteria to investigational rational given lack of clinical evidence to support. Removed toxicity assessment in renewal portion as this is managed by the provider.	02/2020
Previous reviews	10/2019, 10/2018, 06/2018, 03/2018, 12/2017, 09/2017, 06/2017, 03/2017, 12/2016, 09/2016, 07/2016, 07/2015, 09/2014, 04/2014, 02/2013, 06/2012
Policy created	01/2012

Policy Type: PA

Pharmacy Coverage Policy: UMP276

Description

Omaveloxolone (Skyclarys) is a nuclear factor erythroid 2-related factor 2 (Nrf2) activator.

Length of Authorization

- Initial: six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
omaveloxolone (Skyclarys)	Friedreich's ataxia	50 mg capsule	90 capsules/30 days

Initial Evaluation

- I. **Omaveloxolone (Skyclarys)** may be considered medically necessary when the following criteria are met:
 - A. Member is 16 years of age or older; **AND**
 - B. Medication is prescribed by, or in consultation with, a neurologist; **AND**
 - C. A diagnosis of **Friedreich's ataxia** when the following are met:
 1. Documentation of FXN gene mutation; **AND**
 2. Documentation of baseline score from an objective evaluation tool, such as the modified Functional Assessment Rating Scale (mFARS) or Scale for the Assessment and Rating of Ataxia (SARA); **AND**
 3. Provider attestation that the member does not have advanced disease [Note: advanced disease may include loss of multiple physical functionalities such as ability to swallow, speak, walk etc.]; **AND**
 4. The provider attests the member can successfully swallow the capsule whole or contents of the capsule sprinkled on food by mouth (Note: omaveloxolone (Skyclarys) cannot be given via feeding tube)
- II. Omaveloxolone (Skyclarys) is considered investigational when used for all other conditions, including but not limited to:
 - A. Alzheimer's disease
 - B. Amyotrophic lateral sclerosis
 - C. Huntington's disease
 - D. Parkinson's disease
 - E. Progressive supranuclear palsy
 - F. Frontotemporal dementia
 - G. Epilepsy

- H. Malignant melanoma
- I. Non-small cell lung 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. Member has responded to therapy, defined as stability or improvement in net motor function, compared to pretreatment baseline (e.g., stability or improvement in mFARS or SARA scores)

Supporting Evidence

- I. FA (Friedreich's ataxia) is a progressive genetic neurodegenerative disorder that affects nearly 5,000 individuals in the United States. FA is caused by mutations in the frataxin (FXN) gene, which encodes the mitochondrial protein, frataxin. Genetic testing for the triplet repeats expansions in the first intron of the frataxin (FXN) gene that cause Friedreich ataxia should be performed in all patients with progressive cerebellar ataxia and autosomal recessive inheritance. Frataxin deficiency leads to dysregulation of antioxidative defense mechanisms and affects the function of the cerebellum, spinal cord, and peripheral nervous system. FA has been diagnosed in patients two to 50 years old and disease progression is inversely correlated with age of onset. Patients with FA may experience impaired muscle coordination, balance, and speech, loss of coordination, difficulty walking, and impaired muscle coordination, and heart disease. A study evaluating the natural progression of FA found that patients with FA will have on average, a two-point increase in modified FA rating scale (mFARS) score per year.
 - The mFARS score is a series of physical examination assessments to measure disease progression in patients with FA. The mFARS score consists of 4 sections (bulbar function, upper limb coordination, lower limb coordination, upright stability) and ranges from 0-93 points with a higher score indicating worsening disease (e.g. 20-25 at FA diagnosis, ~40 loss of ambulation, 93 indicative of death).
- II. Omaveloxolone is a nuclear factor erythroid 2-related factor 2 (Nrf2) activator and the first FDA-approved treatment for Friedreich's ataxia (FA). The 2022 Friedreich's ataxia clinical management guidelines note that treatment is limited to supportive and symptomatic care in an effort to maintain comfort and function. Guidelines have not been updated to include omaveloxolone (Skyclarys®) in treatment recommendations.
- III. Omaveloxolone was studied in a phase II, multicenter, double-blind, randomized, placebo-controlled trial (MOXIe, part 2) in 103 participants ages 16 to 40 years old with genetically confirmed Friedreich's ataxia (FA) with baseline mFARS scores between 20 to 80. Participants were included if they were able to swallow capsules and complete maximal exercise testing on a recumbent stationary bicycle. Participants with pes cavus (foot morphology with high arch that does not flatten with weightbearing) were allowed in the study but limited to 20% of total subjects enrolled. Patients were excluded if they had uncontrolled diabetes (A1c >11.0%) or clinically significant cardiac disease. Baseline characteristics consistent with more advanced

disease (e.g., longer GAA1 repeat length and history of cardiomyopathy) were more prevalent in the omaveloxolone group. The mean baseline mFARS score was 38 (+/- 11), mean age 23.7 years old, and 92% of all participants were able to ambulate.

- Pes cavus occurs in up to 50-70% of individuals with FA. In MOXle part 1, omaveloxolone improved mFARS in subjects with pes cavus to a lesser degree than those without pes cavus and investigators concluded that participants designated as having pes cavus represented a more severely affected set of individuals with FA.
- The MOXle trial required participants to have the ability to swallow as there was no data around the ability to open omaveloxolone (Skyclarys®) capsules. Additional pharmacokinetic studies have demonstrated that the C_{max} and AUC_{0-inf} were similar when capsule contents were sprinkled on applesauce or when administered as intact capsules. The median T_{max} of omaveloxolone was shortened from approximately 10 to 6 hours when sprinkled on applesauce. Despite a shortened median T_{max}, the dosing regimen remains the same, 150mg orally once daily. Contents of omaveloxolone (Skyclarys®) are not intended to for enteral feeding tube administration.

IV. The primary endpoint of MOXle was change in mFARS score from baseline to week 48. A total of 94 participants completed treatment through week 48; however, those with pes cavus were not included in efficacy analysis (omaveloxolone n=40, placebo n=42). Treatment with omaveloxolone resulted in statistically significant lower mFARS scores (less impairment) relative to placebo at Week 48. The placebo-corrected difference between the two groups was -2.40 points (95% CI, -4.31 to -0.50, p= 0.014). Additionally, a sensitivity analysis for all participants, including those with pes cavus (n= 103), reported a treatment difference of -1.93 +/- 0.90 (95% CI, -3.7, -0.15; p 0.034). Secondary endpoints of change in Patient Global Impression of Change, Clinical Global Impression of Change, 9-HPT: 9-Hole Peg Test, and T25-FW: Timed 25-Foot Walk did not meet statistical significance.

- Validity of the FARS scales have been assessed in many observational studies, demonstrating its high correlation with age of onset, genetic burden of disease. There is no clinically meaningful threshold in reduction of mFARS scores. The SARA scale is an 8-item performance scale used to assess ataxia (gait, stance, sitting, speech disturbances, finger chase, hand movement, extremity kinetics, etc). It ranges from 0 to 40 (40 indicative of severe ataxia). Both mFARS and SARA scales may be used in practice. SARA is a timelier assessment compared to mFARS and scores from each assessment cannot be directly compared.
- The FDA accepts mFARS as an appropriate primary endpoint in clinical trials, however, request that additional patient-reported or performance-based outcome endpoints are also assessed.

V. All participants included in analysis experienced mild to moderate adverse events. Safety was similar between the active and placebo groups. The most common adverse events reported for omaveloxolone included contusion (37%), headache (25%), upper respiratory tract infection (29%), excoriation (23%), and nausea (14%).

VI. Participants who completed MOXle part 2 were eligible to enroll in a non-inferiority open-label extension study (up to 144 weeks of total treatment). A total of 73 individuals enrolled in the extension study, including 39 participants who were initially randomized to placebo (placebo-

omaveloxolone group) and 34 initially randomized to omaveloxolone (omaveloxolone-omaveloxolone group). Participants received omaveloxolone 150mg once daily. The difference in mFARS between omaveloxolone and placebo observed at the end of placebo-controlled MOXIe part 2 (least squared (LS) mean difference -2.17 +/- 1.09 points, $p=0.0471$).

- VII. The quality of evidence is considered moderate given a well-designed randomized clinical trial with supporting OLE data reporting consistent improvement in mFARS scores. Omaveloxolone demonstrated significant reduction in mFARS score; however, there is currently no standard clinically meaningful threshold for improvement in mFARS score. Although time-specific, the change in mFARS is directly correlated with age of onset, genetic burden of disease, and patient reported outcomes. Similarly, a reduction in mFARS may be indicative of disease stability. Generalizability of current clinical data may be limited due to exclusion of patients with severe disease (mFARS > 80), non-ambulatory patients and those with pre-existing cardiac conditions. However, for the majority of patients with mild to moderate FA, omaveloxolone (Skyclarys) may provide a potential clinical benefit. It is unclear if omaveloxolone will deliver similar responses outside of the clinical trial setting.

Investigational or Not Medically Necessary Uses

- I. Omaveloxolone (Skyclarys) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Reata Pharmaceuticals noted that the MOXIe trial provided proof of concept for use of omaveloxolone in other neurological diseases where mitochondrial dysfunction and neuroinflammation are common features. Reata has observed activity in preclinical models.
 - i. Alzheimer's disease
 - ii. Amyotrophic lateral sclerosis
 - iii. Huntington's disease
 - iv. Parkinson's diseases
 - v. Progressive supranuclear palsy
 - vi. Frontotemporal dementia
 - vii. Epilepsy
 - B. Malignant melanoma
 - i. Omaveloxolone was previously evaluated in a phase 1b/2 non-randomized, open-label trial as adjunct to ipilimumab or nivolumab in stage 3/4 malignant melanoma. The primary outcome was overall response rate and 23 out of 34 participants had a response.
 - C. Non-small cell lung cancer
 - i. Omaveloxolone was previously evaluated in a phase 1 study in patients with metastatic or incurable non-small cell lung cancer or melanoma. Omaveloxolone did not prevent disease progression.

References

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1. Skyclarys (omaveloxolone) [prescribing information]. Plano, TX: Reata Pharmaceuticals Inc; February 2023.
2. Lynch DR, Chin MP, Delatycki MB, et al. Safety and Efficacy of Omaveloxolone in Friedreich Ataxia (MOXIe Study). *Ann Neurol*. 2021;89(2):212-225.
3. Lynch DR, Chin MP, Boesch S, et al. Efficacy of Omaveloxolone in Friedreich's Ataxia: Delayed-Start Analysis of the MOXIe Extension. *Mov Disord*. 2023;38(2):313-320.
4. Lynch DR, et al. Safety, pharmacodynamics, and potential benefit of omaveloxolone in Friedreich ataxia. *Ann Clin Transl Neurol*. 2018;6(1):15–26.
5. Corben LA, Collins V, Milne S, et al. Clinical management guidelines for Friedreich ataxia: best practice in rare diseases. *Orphanet J Rare Dis*. 2022;17(1):415. Published 2022 Nov 12.
6. Rummey C, Corben LA, Delatycki MB, et al. Psychometric properties of the Friedreich Ataxia Rating Scale. *Neurol Genet*. 2019;5(6):371. Published 2019 Oct 29.
7. Rummey C, Zesiewicz TA, Perez-Lloret S, Farmer JM, Pandolfo M, Lynch DR. Test-retest reliability of the Friedreich's ataxia rating scale. *Ann Clin Transl Neurol*. 2020;7(9):1708-1712.
8. Patel M, Isaacs CJ, Seyer L, et al. Progression of Friedreich ataxia: quantitative characterization over 5 years. *Ann Clin Transl Neurol*. 2016;3(9):684-694. Published 2016 Jul 25.
9. Muscular Dystrophy Association. Friedreich's ataxia (FA). Accessed August 4, 2022. <https://www.mda.org/disease/friedreichs-ataxia>.
10. National Institutes of Health (NIH). National Institute of Neurological Disorders and Stroke (NINDS). Friedreich's ataxia fact sheet. June 2018. Accessed August 4, 2022.

Related Policies

Currently there are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated criteria requiring ability to swallow capsules whole to reflect new pharmacokinetic data revealing omaveloxolone (Skyclarys®) may be opened and sprinkled on applesauce. Supporting evidence was updated to reflect rewording of criteria.	05/2024
Policy created	05/2023

Policy Type: PA

Pharmacy Coverage Policy: UMP173

Description

To combat the opioid use disorder in Washington State.

Length of Authorization

- Initial: up to 12 months
- Renewal: up to 12 months

Fill limitations not requiring attestation

Short-Acting Opioids			
- A quantity limit of 18 dosages per prescription for children (ages 20 and under) - A quantity limit of 42 dosages per prescription for adults (ages 21 and older)			
Note: Prescriber indicating EXEMPT overrides the quantity			
Active ingredients containing*			
Combination products containing any of these listed ingredients are included in this policy			
morphine sulfate	codeine sulfate	hydromorphone	oxymorphone
hydrocodone	levorphanol	meperidine	oxycodone
pentazocine	tapentadol	tramadol	butorphanol

Long-Acting Opioids			
All quantity and duration requires a signed attestation			
Active ingredients containing**			
Combination products containing any of these listed ingredients are included in this policy			
morphine sulfate	codeine sulfate	hydromorphone	oxymorphone
oxycodone	fentanyl patches	tramadol	hydrocodone
tapentadol			

*Please note – acetaminophen products are limited to 4000 mg per day

‡Includes Extended release (ER) formulations as well as short acting or immediate release (IR) formulation use beyond 6 weeks.

Initial Evaluation

- Chronic opioid use attestation form MUST be filled out and sent in for approval. This form can be found here: <https://www.hca.wa.gov/assets/pebb/ump-opioid-attestation-form.pdf>; **AND**
- When use is beyond the quantity limits and duration listed above, or total Morphine Milligram Equivalent (MME) per day is 120 or greater, the following attestation agreement is required:

Criteria for chronic use of opioids or high-dose opioids for the treatment of pain not relating to active cancer treatment, hospice care, palliative care, end-of-life care, or sickle cell disease:

- The need for chronic opioid use (more than 42 days per 90-day calendar period or use of long-acting opioids) and/or high dose opioids (≥ 120 MMEs per day) is medically necessary and is documented in the medical record; **AND**
- The patient is currently using or has tried and failed appropriate non-opioid medications, and/or non-pharmacologic therapies; **AND**
- The provider has recorded baseline and ongoing assessments of measurable, objective pain

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scores and function scores. These should be tracked serially in order to demonstrate clinically meaningful improvements in pain and function; **AND**

4. The patient has been screened for mental health disorders, substance use disorder, and naloxone use; **AND**
5. The provider has or will conduct periodic urine drug screens; **AND**
6. The provider has checked the PMP for any other opioid use and concurrent use of benzodiazepines and other sedatives; **AND**
7. If opioids are being prescribed by any other prescriber, the provider has coordinated care with the other prescriber; **AND**

INDICATE WHICH APPLIES:

☐ **For chronic opioid use:**

- The patient must be using or had trials of short-acting opioid therapy for at least 42 days; **OR**
- The reason for inadequate response to short-acting opioid therapy is documented in the medical record; **OR**
- Justification of beginning an opioid naïve patient on a long-acting opioid is documented in the medical record;

☐ **For high-dose opioids (≥ 120 MME per day):**

- The provider is a pain management specialist as defined in WAC 246-919-945; **OR**
 - The provider successfully completed a minimum of twelve category 1 continuing education hours on chronic pain management within the previous four years and at least two of these hours were dedicated to substance use disorders; **OR**
 - The provider is a pain management physician working in a multidisciplinary chronic pain treatment center or a multidisciplinary academic research facility; **OR**
 - The provider has a minimum of three years of clinical experience in a chronic pain management setting, and at least thirty percent of the providers current practice is the direct provision of pain management care; **OR**
 - The provider has consulted with a pain management specialist regarding use of high dose opioids (≥ 120 MME per day) for this patient which is documented in the medical record; **OR**
 - The patient is following a tapering schedule with a starting dose ≥ 120 MME per day; **AND**
8. The provider has discussed with the patient the realistic goals of pain management therapy and has discussed discontinuation as an option during treatment; **AND**
 9. The provider confirms that the patient understands and accepts these conditions, and the patient has signed a pain contract or informed consent document.

I attest that all of the above criteria are met, or there is documentation in patient's chart for why one or more are not applicable ☐ Yes ☐ No

The requested treatment is medically necessary, does not exceed the medical needs of the member, and is clinically supported in the member's medical record ☐ Yes ☐ No

When should this treatment plan expire? Please specify date in MM/DD/YYYY format: _____

Note: The attestation form will expire on the date specified above or 12 months after the date of signature, whichever is soonest.

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Renewal Evaluation

- I. See initial evaluation section.

Supporting Evidence

- I. The policy aligns with recommendations of the Centers for Disease Control, the Washington State Agency Medical Directors Group, and the Bree Collaborative around safe and appropriate opioid prescribing.
- II. This is a Uniform Medical Plan (UMP) mandated criteria on all opioid policies.
This policy is in full compliance with UMP's regulations and mandates regarding the chronic use of opioids.
- III. This policy applies to all groups under UMP, including Public Employees Benefit Board (PEBB) and School Employees Benefits Board (SEBB).

Investigational or Not Medically Necessary Uses

- I. Chronic use of any opioid beyond 42-days within a 90-day period without a signed attestation from the prescribing provider on file.

References

1. Washington State Agency Medical Directors Group. Interagency Guideline on Prescribing Opioids for Pain. 3rd Edition, June 2015. Available: www.agencymeddirectors.wa.gov/Files/2015AMDGOpioidGuideline.pdf

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated attestation to include new MME requirements	08/2023
Updated to include QLs not requiring attestation as well as updating chronic attestation and high dose attestation requirements effective 7/1/2023	07/2023
Added APAP limit wording to QL box	03/2020
Creation of policy	02/2020

Policy Type: PA

Pharmacy Coverage Policy: UMP144

Description

Methylnaltrexone bromide (Relistor), naldemedine (Symproic), and naloxegol (Movantik) are orally administered mu-opioid antagonists that act specifically in the peripheral tissues with inhibited central nervous system penetration at recommended dosages.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
methylnaltrexone bromide (Relistor)	150 mg tablets	Treatment of opioid-induced constipation in adults with chronic non-cancer pain	90 tablets/30 days
	12 mg vial/syringe	Treatment of opioid-induced constipation with advanced illness or pain caused by active cancer requiring opioid dosage escalation	30 single use vials or syringes/30 days
	8 mg vial/syringe		30 single use vials or syringes/30 days
naldemedine (Symproic)	0.2 mg tablets	Treatment of opioid-induced constipation in adults with chronic non-cancer pain	30 tablets/30 days
naloxegol (Movantik)	12.5 mg tablets		30 tablets/30 days
	25 mg tablets		30 tablets/30 days

Initial Evaluation

- I. **Methylnaltrexone bromide (Relistor), naldemedine (Symproic), and naloxegol (Movantik)** may be considered medically necessary when the following criteria below are met:
 - A. Member is 18 years of age or older; **AND**
 - B. Diagnosis of **Opioid-Induced Constipation (OIC)** when the following are met:
 1. Treatment with at least one agent from the following has been ineffective, contraindicated, or not tolerated:
 - i. Stool softener (e.g. docusate sodium); **OR**
 - ii. Osmotic agent (e.g. polyethylene glycol); **OR**
 - iii. Stimulant laxative (e.g. sennoside); **AND**
 2. If the request is for **methylnaltrexone bromide (Relistor)**:
 - i. Treatment with all of the following has been ineffective, contraindicated, or not tolerated:
 - a. naloxegol (Movantik); **AND**

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b. naldemedine (Symproic)

- II. Methylnaltrexone (Relistor), naldemedine (Symproic) and naloxegol (Movantik) are considered investigational when used for all other conditions, including but not limited to:
- A. Constipation not induced by opioids
 - B. Post-operative ileus

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**
- III. Initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
- IV. Member is continuing to receive chronic opioids; **AND**
- V. Member has shown an improvement in the number of bowel movements they are having

Supporting Evidence

- I. The American Gastroenterological Association (AGA) guidelines recommend the use of naloxegol (Movantik) and naldemedine (Symproic) for laxative-resistant patients with OIC. Methylnaltrexone bromide (Relistor) was given a conditional recommendation for laxative-resistant patients with OIC as the evidence was considered low quality. The AGA did not make a recommendation for lubiprostone (Amitiza®) as the evidence was low quality and inconsistent, with one trial not showing any statistical difference from placebo.
- II. Methylnaltrexone bromide (Relistor) was studied in four trials compared against placebo. Patients were not on any background therapies in studies one and two. Studies four and five allowed patients to continue on their regular laxative regimen. The evidence is considered low quality with some studies having high rates of dropout and endpoints evaluated in studies four and five having unknown clinical benefit for patients.
 - Study one and two were randomized, double-blind, placebo-controlled trials evaluating 713 patients with OIC and chronic non-cancer pain. Methylnaltrexone bromide (Relistor) tablets and injection demonstrated a statistically significant response for proportion of responders compared to placebo. The percent difference was 13% (CI 3%, 23%) for study one and 20% (CI 10%, 31%) for study two.
 - Study three was a long-term, open-label, uncontrolled trial looking at 1,034 patients with OIC and chronic non-cancer pain. Safety was the primary endpoint with the most common adverse events being abdominal pain, diarrhea, nausea, and psychiatric disorders. The mean change in bowel movements from baseline was 1.5 bowel movements per week ($p < 0.001$).
 - Study four and five were double-blind, placebo-controlled trials evaluating 287 patients with OIC and advanced illness (patients receiving palliative opioid therapy). Methylnaltrexone bromide (Relistor) injection demonstrated a statistically

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significant improvement in the proportion of patients with a rescue-free laxation within four hours of study medication compared to placebo. Results from study four were 62%, 58%, 14% ($p<0.0001$) for the 0.15 mg/kg dose, 0.3 mg/kg dose, and placebo, respectively, and study five results were 48% and 16% ($p<0.0001$) for methylnaltrexone bromide (Relistor) and placebo, respectively.

- III. Naloxegol (Movantik) was studied in two randomized, double-blind, placebo-controlled trials in patients with OIC and chronic non-cancer pain. The primary endpoint for both studies evaluated response to therapy defined as ≥ 3 spontaneous bowel movements (SBMs) per week and a change from baseline of ≥ 1 SBM per week for at least nine out of the 12 study weeks and three out of the last four study weeks.
 - Study one and two evaluated 1,352 patients comparing 12.5 mg and 25 mg of naloxegol (Movantik) against placebo. There was a statistically significant difference for both strengths compared to placebo in study one and only the 25 mg strength in study two. A treatment difference of 11.4% (2.4%, 20.4%) and 15% (5.9%, 24%) for 12.5 mg and 25 mg, respectively, was seen in study one and 10.3% (1.7%, 18.9%) in study two.
- IV. Naldemedine (Symproic) was studied in four randomized, double-blind, placebo-controlled trials looking at patients with OIC and chronic non-cancer pain. The primary endpoint for both studies evaluated response to therapy defined as ≥ 3 SBMs per week and a change from baseline of ≥ 1 SBM per week for at least nine out of the 12 study weeks and three out of the last four study weeks.
 - Study one and two were 12 week trials evaluating 1,080 patients comparing 0.2 mg of naldemedine (Symproic) against placebo. There was a statistically significant difference for naldemedine (Symproic) compared to placebo with a treatment difference of 13% (CI 5%, 21%) for study one and 19% (CI 11%, 27%) for study two.
 - Study three was a 52 week trial evaluating 1246 patients comparing 0.2 mg of naldemedine (Symproic) against placebo. The primary outcome measured was treatment emergent adverse events which did not have any difference between treatment arms. There was sustained improvement in bowel movement frequency for naldemedine (Symproic) compared to placebo ~ 3.5 vs ~ 2.5 , respectively ($p<0.0001$).
 - Naldemedine (Symproic) was compared against placebo in a two week, randomized, double-blind, placebo-controlled trial with an open-label 12 week extension evaluating 193 patients with active cancer. Naldemedine (Symproic) had a statistically significant difference over placebo for the primary endpoint of proportion of SBM responders with a treatment difference of 36.8% (CI 23.7%, 49.9%).

Investigational or Not Medically Necessary Uses

- I. These therapies have not been studied in the following conditions:
 - A. Constipation not induced by opioids
 - B. Post-operative Ileus

References

1. Relistor [Prescribing Information]. Bridgewater, NJ: Salix Pharmaceuticals, Inc. November 2018.
2. Movantik [Prescribing Information]. Wilmington, DE: AstraZeneca Pharmaceuticals. May 2019.
3. Symproic [Prescribing Information]. Raleigh, NC: BioDelivery Sciences International, Inc. April 2019.
4. Uptodate, Inc. Prevention and management of side effects in patients receiving opioids for chronic pain [database online]. Waltham, MA. Updated 11/11/19. Available at: <http://www.uptodate.com/home/index.html>. [Accessed 11/19/19].
5. Crockett SD, Greer KB, Heidelbaugh JJ, Falck-Ytter Y, Hanson BJ, Sultan S. American Gastroenterological Association Institute Guideline on the Medical Management of Opioid-Induced Constipation. *Gastroenterology*. 2019;156(1):218-226.
6. Webster LR, Michna E, Khan A, Israel RJ, Harper JR. Long-Term Safety and Efficacy of Subcutaneous Methylnaltrexone in Patients with Opioid-Induced Constipation and Chronic Noncancer Pain: A Phase 3, Open-Label Trial. *Pain Med*. 2017;18(8):1496-1504.
7. Webster LR, Nalamachu S, Morlion B, et al. Long-term use of naldemedine in the treatment of opioid-induced constipation in patients with chronic noncancer pain: a randomized, double-blind, placebo-controlled phase 3 study. *Pain*. 2018;159(5):987-994.
8. Katakami N, Harada T, Murata T, et al. Randomized Phase III and Extension Studies of Naldemedine in Patients With Opioid-Induced Constipation and Cancer. *J Clin Oncol*. 2017;35(34):3859-3866.

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated criteria for Movantik and Symproic from requiring trial and failure of two OTC alternatives to one	01/2022
Transitioned criteria to policy: removed required trial and failure of lubiprostone (Amitiza) for all agents	11/2019
Previous Reviews	01/2018; 02/2018; 03/2018

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP017

Description

Deferasirox (Exjade, Jadenu), and deferiprone (Ferroprox) are orally administered iron chelating agents.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
deferasirox (generic Exjade)	125 mg tablet for suspension	Hemosiderosis (chronic iron overload) – non-transfusion related thalassemia syndrome	Non-transfusion thalassemia syndrome: Monthly quantity to allow for a maximum of 20 mg/kg per day
	250 mg tablet for suspension		
	500 mg tablet for suspension		
deferasirox (Exjade)	125 mg tablet for suspension	Hemosiderosis (chronic iron overload) – transfusion thalassemia	Setting of transfusions: Monthly quantity to allow for a maximum of 40 mg/kg per day
	250 mg tablet for suspension		
	500 mg tablet for suspension		
deferasirox (generic Jadenu)	90 mg tablet	Hemosiderosis (chronic iron overload) – non-transfusion related thalassemia syndrome	Non-transfusion thalassemia syndrome: Monthly quantity to allow for a maximum of 14 mg/kg per day
	180 mg tablet		
	360 mg tablet		
	90 mg granule		
	180 mg granule		
	360 mg granule		
deferasirox (Jadenu)	90 mg tablet	Hemosiderosis (chronic iron overload) – transfusion thalassemia	Setting of transfusions: Monthly quantity to allow for a maximum of 28 mg/kg per day
	180 mg tablet		
	360 mg tablet		
	90 mg granule (sprinkle)		
	180 mg granule (sprinkle)		
	360 mg granule (sprinkle)		
	500 mg tablet	Hemosiderosis	

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deferiprone (generic Ferriprox)	1000 mg tablet	(chronic iron overload) – transfusion thalassemia and transfusions related to sickle cell disease or other anemias	Monthly quantity to allow for a maximum of 99 mg/kg per day
deferiprone (Ferriprox)	100 mg/1 mL solution		
	80 mg/1mL solution		
	500 mg tablet		
	1000 mg tablet		

Initial Evaluation

- I. **Deferasirox (Exjade, Jadenu), and deferiprone (Ferriprox)** may be considered medically necessary when the following criteria below are met:
 - A. Prescribed by, or in consultation with, a specialist (e.g., hematologist); **AND**
 - B. Documentation of the members weight that has been measured in the past three months; **AND**
 - C. A diagnosis of one of the following:
 1. **Chronic iron overload due to non-transfusion dependent thalassemia (NTDT) syndromes; AND**
 - i. Member is ten years of age or older; **AND**
 - ii. Documentation of a liver iron (Fe) concentration (LIC) of at least 5 mg per gram of dry weight; **AND**
 - iii. Documentation serum ferritin levels are greater than 300 mcg/L; **AND**
 - iv. Generic deferasirox (generic for Exjade OR Jadenu) has been prescribed; **OR**
 - a. Brand Exjade or Jadenu is prescribed and **both** generic deferasirox (generic for Exjade) AND deferasirox (generic for Jadenu) have been ineffective or contraindicated (disliking taste of the tablet suspension is not considered for inefficacy or contraindication) (Please note: deferiprone [Ferriprox] is not FDA-approved for this indication); **OR**
 2. **Chronic iron overload due to blood transfusions; AND**
 - i. Member is two years of age or older and brand or generic deferasirox (Exjade) or deferasirox (Jadenu) are prescribed; **OR**
 - a. Member is eight years of age or older and deferiprone (Ferriprox) tablets are prescribed; **OR**
 - b. Member is three years of age or older and deferiprone (Ferriprox) solution is prescribed; **AND**
 - ii. Documentation is provided that the member has received transfusions that have resulted in consistent serum ferritin level greater than 1000 mcg/L; **OR**

- a. Documentation is provided that the member has received transfusions that have resulted in liver iron concentration (LIC) $\geq 5\text{mg/g}$ dry weight (dw); **AND**
 - iii. Generic deferasirox (generic for Exjade OR Jadenu) has been prescribed; **OR**
 - a. Brand Exjade, Jadenu, or generic deferiprone (Ferriprox) is prescribed and **both** generic deferasirox (generic for Exjade) AND deferasirox (generic for Jadenu) have been ineffective or contraindicated (disliking taste of the tablet suspension is not considered for inefficacy or contraindication)
 - b. Brand Ferriprox is prescribed and **both** generic deferasirox (generic for Exjade) **AND** deferasirox (generic for Jadenu) **AND** generic deferiprone have been ineffective or contraindicated (disliking taste of the tablet suspension is not considered for inefficacy or contraindication)
- II. Deferasirox (Exjade), deferasirox (Jadenu) and deferiprone (Ferriprox) are considered not medically necessary when criteria above are not met and/or when used for:
 - A. Plasmodium falciparum parasitemia
- III. Deferasirox (Exjade), deferasirox (Jadenu) and deferiprone (Ferriprox) are considered investigational when used for all other conditions, including but not limited to:
 - A. Hereditary hemochromatosis
 - B. Porphyria cutanea tarda

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 the member's weight, measured in the past three months; **AND**
 - A. **Chronic iron overload due to non-transfusion dependent thalassemia syndromes; AND**
 - 1. Documentation of a serum ferritin levels are greater than 300 mcg/L; **AND**
 - 2. Generic deferasirox (generic for Exjade OR Jadenu) has been prescribed; **OR**
 - i. Brand Exjade or Jadenu is prescribed and **both** generic deferasirox (generic for Exjade) AND generic deferasirox (generic for Jadenu) have been ineffective or contraindicated (disliking taste of the tablet suspension is not considered for inefficacy or contraindication) (deferiprone [Ferriprox] is not FDA-approved for this indication); **AND**
 - 3. A response to treatment, defined by a decline in serum ferritin level OR liver iron concentration (LIC), has been documented; **OR**

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B. Chronic iron overload due to blood transfusions; AND

- a. Documentation that the member is continuing to receive transfusions resulting in serum ferritin levels consistently greater than 500 mcg/L; **AND**
- b. Generic deferasirox (generic for Exjade OR Jadenu) has been prescribed; **OR**
 - i. Brand Exjade, Jadenu, or generic deferiprone (Ferriprox) is prescribed and **both** generic deferasirox (generic for Exjade) AND generic deferasirox (generic for Jadenu) have been ineffective or contraindicated (disliking taste of the tablet suspension is not considered for inefficacy or contraindication); **OR**
 - ii. Brand Ferriprox is prescribed and both generic deferasirox (generic for Exjade) AND deferasirox (generic for Jadenu) AND generic deferiprone have been ineffective or contraindicated (disliking taste of the tablet suspension is not considered for inefficacy or contraindication); **AND**
- c. A response to treatment, defined by a decline in serum ferritin level OR liver iron concentration (LIC), has been documented

Supporting Evidence

- I. The agents listed in this policy are iron chelating agents indicated for chronic iron overload but have not been shown to improve survival or disease-related symptoms. Of note, the products are not interchangeable on a dose basis. Deferiprone (Ferriprox) is an iron chelator indicated only for transfusional iron overload in patients with thalassemia, sickle cell disease, or other anemias. Although deferiprone (Ferriprox) was previously reserved for use when other chelation therapy had been inadequate, labeling has been updated to no longer require use of other chelation therapy prior to therapy with deferiprone (Ferriprox). Deferasirox (Exjade, Jadenu) remains the most cost-effective therapy in this class; the requirement of trial and failure of therapy with deferasirox (Exjade, Jadenu) prior to coverage of deferiprone (Ferriprox) has been maintained in this policy.
- II. Per the package inserts for the medications listed in this policy, doses are based on weight. Safety and efficacy of the medications have been studied for FDA-approved weight-based doses. Doses escalation beyond these limits has not been evaluated.
- III. Clinical trials evaluated deferasirox (Exjade) and deferasirox (Jadenu) in patients 10 years of age or older for chronic iron overload due to non-transfusion dependent thalassemias, and for two years of age or older for iron overload due to blood transfusions. Deferiprone (Ferriprox) has not been adequately evaluated for safety and efficacy in patients younger than eight years of age for the tablet formulation and three years of age for the solution formulation.
- IV. **Chronic iron overload due to non-transfusion dependent thalassemia (NTDT) syndromes**
 - For iron overload not due to transfusion, deferasirox (Exjade) and deferasirox (Jadenu) were studied in patients with an LIC of at least 5 mg of iron per dry weight and a serum ferritin greater than 300 mcg/L. Levels of serum ferritin below 300 mcg/L are considered within normal range and would not meet medical necessity for dosing of iron overload treatment products.
- V. **Chronic iron overload due to blood transfusions**

- Although deferasirox (Exjade, Jadenu) has not been approved in chronic iron overload in patients with sickle cell disease specifically, there is evidence of clinical benefit in this indication. Deferasirox (Exjade, Jadenu) was studied in one phase 2, randomized, open-label trial in comparison to deferoxamine in 195 patients age two and older with sickle cell disease and transfusional hemosiderosis. At end of study, the mean change in LIC in the per protocol-1 (PP-1) population, which consisted of patients who had at least 1 post-baseline LIC assessment, was -1.3 mg Fe/g dry weight for patients receiving deferasirox tablets for oral suspension (n = 113) and -0.7 mg Fe/g dry weight for patients receiving deferoxamine (n = 54).
 - For iron overload due to transfusion in patients with sickle cell disease and other anemias, deferiprone (Ferriprox) was studied in one randomized, controlled, open-label, non-inferiority trial against deferoxamine in 228 patients age two and older. The primary endpoints were change from baseline in liver iron concentration (LIC) at 12 months; the non-inferiority criteria was met with a mean decrease from baseline in LIC of 4.04 ± 0.48 mg/g dw (deferiprone) vs. 4.45 ± 0.57 mg/g dw (deferoxamine). Adverse drug reactions (ADRs) observed during the clinical trial were consistent with those already seen in the thalassemia population. The rates of agranulocytosis were also comparable to those seen in patients with thalassemia; no new safety signals or concerns were noted.
- VI. For transfusion related iron overload, patient with a serum ferritin level greater than or equal to 1000 mcg/L or a liver iron concentration of 3 to 5 mg/g dry weight (dw), or higher, will be considered for iron overload products. Upon renewal, patients with a serum ferritin level below 500 mcg/L will have therapy temporarily discontinued.
- VII. As of December 2019, AB-rated generics for Exjade and Jadenu tablets were available on the market.
- VIII. As of February 2021, AB-rated generics for Ferriprox 500mg tablets were available on the market. All other strengths and dosage forms remain available in the Brand formulation only.

Investigational or Not Medically Necessary Uses

- I. Plasmodium falciparum parasitemia
 - A. In a prospective, double-blind, placebo-controlled trial, deferiprone was found to be clinically ineffective against plasmodium falciparum parasitemia.
- II. Hereditary hemochromatosis and porphyria cutanea tarda
 - A. Clinical trials are investigating iron overload agents in these settings.

References

1. Exjade [Prescribing Information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation. May, 2018.
2. Jadenu [Prescribing Information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation. May, 2018.
3. Ferriprox [Prescribing Information]. Toronto, Ontario, Canada. Apotex Inc. April, 2021.
4. Cohen AR, Glimm E, Porter JB. Effect of transfusional iron intake on response to chelation therapy in beta-thalassemia major. Blood. 2008;111(2):583-7.

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5. Taher AT, Porter JB, Viprakasit V, et al. Deferasirox demonstrates a dose-dependent reduction in liver iron concentration and consistent efficacy across subgroups of non-transfusion-dependent thalassemia patients. *Am J Hematol.* 2013;88(6):503-6.
6. Vichinsky E, Onyekwere O, Porter J, et al. A randomised comparison of deferasirox versus deferoxamine for the treatment of transfusional iron overload in sickle cell disease. *Br J Haematol.* 2007;136(3):501-8.
7. Tricta F, Uetrecht J, Galanello R, et al. Deferiprone-induced agranulocytosis: 20 years of clinical observations. *Am J Hematol.* 2016;91(10):1026-31.
8. Elalfy M, et al. Deferiprone versus deferoxamine for transfusion-dependent anemias (FIRST study). Chiesi [unpublished].
9. Elalfy M, et al. Long-term efficacy and safety of deferiprone for patients with sickle cell disease or other anemias (FIRST-EXT study). Chiesi [unpublished].

Policy Implementation/Update:

Action and Summary of Changes	Date
Added 1000mg strength of deferiprone (generic Ferriprox)	02/2022
Addition of generic deferasirox oral granules and generic deferiprone tablets to policy; requirement to have trial and failure or contraindication to both generic Exjade and Jadenu for prior to payment consideration of generic deferiprone, and generic Exjade and Jadenu AND generic deferiprone prior to payment consideration for brand Ferriprox. Criteria updated regarding the following: age for use of deferiprone tablets (8 years old) and deferiprone solution (3 years old), addition of LIC as baseline and renewal measurement for transfusional iron overload. Update to supporting evidence.	09/2021
Addition of generic Jadenu and new strength of deferiprone to the policy, with requirement to have trial and failure or contraindication, to both generic Exjade and Jadenu prior to payment consideration for brand products of this policy.	12/2019
Iron chelating agent policies combined, criteria added regarding the following: weight documentation, ferritin level documentation, addition of a policy to Jadenu, specialist prescribing, additional of generic deferasirox (Exjade) tablet for oral suspension and step through this product. Transition to policy format.	05/2019
Criteria created	08/2013

Policy Type: PA

Pharmacy Coverage Policy: UMP045

Description

Ospemifene (Osphena) is an orally administered estrogen agonist and antagonist.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
ospemifene (Osphena)	Moderate to severe dyspareunia due to vulvar and vaginal atrophy associated with menopause; Moderate to severe vaginal dryness due to vulvar and vaginal atrophy associated with menopause	60 mg tablets	30 tablets/30 days

Initial Evaluation

- I. **Ospemifene (Osphena)** may be considered medically necessary when the following criteria below are met:
 - A. A diagnosis of **moderate to severe vaginal dryness; AND**
 1. Member is being treated for vaginal dryness as a symptom of vulvar and vaginal atrophy, due to menopause; **AND**
 2. Treatment with the following has been ineffective, contraindicated, or not tolerated:
 - i. One systemic hormone replacement therapy (e.g., estradiol oral tablets, estradiol patch, estradiol injection); **AND**
 - ii. One vaginal hormone replacement therapy (e.g., Estring, generic estradiol cream)
- II. Ospemifene (Osphena) is an excluded medication when the following criteria below are met:
 - A. A diagnosis of **moderate to severe dyspareunia** (difficult or painful sexual intercourse) as a symptom of vulvar and vaginal atrophy, due to menopause

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. Request is for a diagnosis of moderate to severe vaginal dryness; **AND**
- IV. Member has exhibited improvement or stability of disease symptoms [e.g., decreased genital dryness, burning, irritation, urinary symptoms of urgency, dysuria, and recurrent UTIs]

Supporting Evidence

- I. Genitourinary syndrome of menopause (GSM) is defined as a collection of symptoms and signs caused by hypoestrogenic changes to the labia majora/minora, clitoris, vestibule/introitus, vagina, urethra, and bladder that occur in menopausal patients. The term GSM was introduced by the International Society for the Study of Women's Sexual Health and the North American Menopause Society in 2014 and replaced the term vaginal atrophy (other terms include vulvovaginal atrophy, urogenital atrophy, or atrophic vaginitis).
- II. Vaginal atrophy is a direct consequence of the hypoestrogenic state associated with menopause resulting in anatomic and physiologic changes in the genitourinary tract. The North American Menopause Society estimates that 10–40% of menopausal women will experience one or more symptoms of vaginal atrophy. Vaginal atrophy causes bothersome vaginal symptoms commonly associated with menopause including, vaginal or vulvar dryness, discharge, itching, and dyspareunia. A loss of superficial epithelial cells in the genitourinary tract causes thinning of tissue. Loss of vaginal rugae and elasticity occur with a narrowing and shortening of the vagina. Epithelial tissues are more fragile and may tear, leading to bleeding and fissures. There also is a loss of subcutaneous fat in the labia majora. These changes result in narrowing of the introitus, fusion of the labia minora, and shrinking of the clitoral prepuce and urethra. Vaginal pH becomes more alkaline, which may alter the vaginal flora and increase the risk of urogenital infection.
- III. American College of Obstetricians and Gynecologist (ACOG) stated in their Clinical Guidelines on Management of Menopausal Symptoms that vaginal symptoms (e.g., dyspareunia, vaginal or vulvar dryness, discharge, itching) are best treated with systemic or topical hormone therapy. These guidelines recommend both systemic and vaginal/local estrogen preparations.
- IV. The 2022 hormone therapy position statement of The North American Menopause Society attest hormone therapy remains the most effective treatment for vasomotor symptoms (VMS) and the genitourinary syndrome of menopause and has been shown to prevent bone loss and fracture. The risks of hormone therapy differ depending on type, dose, duration of use, route of administration, timing of initiation, and whether a progestogen is used. Treatment should be individualized using the best available evidence to maximize benefits and minimize risks, with periodic reevaluation of the benefits and risks of continuing therapy. For bothersome genitourinary syndrome of menopause symptoms not relieved with over-the-counter therapies in women without indications for use of systemic hormone therapy, low-dose vaginal estrogen therapy or other therapies (eg, vaginal dehydroepiandrosterone or oral ospemifene) are recommended.
- V. Dyspareunia is defined as difficult or painful sexual intercourse. Ospemifene (Osphena) for dyspareunia, a form of sexual dysfunction is in a category of medications that are not covered

under the prescription benefit. Drugs used for sexual dysfunction are excluded from coverage. Please reference the member handbook/certificate of coverage for further information regarding this denial.

References

1. Oregon Insurance Division Bulletin INS 2014-1 Mental Health Parity.
2. Diagnostic and Statistical Manual of Mental Disorders (DSM) Versions IV-TR and V.
3. Osphena [prescribing information]. Shionogi Inc.: Florham Park, NJ; January 2019
4. Gracia C. The American College of Obstetricians and Gynecologist Clinical Guidelines on Management of Menopausal Symptoms. Am Fam Physician. 2014; 90(5):338-340.
5. The 2022 Hormone Therapy Position Statement of The North American Menopause Society” Advisory Panel. The 2022 hormone therapy position statement of The North American Menopause Society. Menopause. 2022;29(7):767-794.

Related Policies

Currently there are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated supporting evidence to reflect new guideline updates from the 2022 hormone therapy position statement of the North American Menopause Society. Updated quantity limit table and renewal criteria to standard formatting.	07/2023
Updated policy to remove coverage in the setting of dyspareunia as this is an excluded benefit.	09/2019
Converted criteria to the new policy format. Added newly FDA approved indication of moderate to severe vaginal dryness due to vulvar and vaginal atrophy associated with menopause. The route for approval in the setting of vaginal dryness follows the ACOG Clinical Guidelines.	03/2019

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP261

Description

Oteseconazole (Vivjoa) is an orally administered azole antifungal.

Length of Authorization

- Initial: Three months
- Renewal: Cannot be renewed

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
oteseconazole (Vivjoa)	Recurrent vulvovaginal candidiasis (RVVC) in females of non-reproductive potential	150mg capsules	18 capsules/84 days

Initial Evaluation

- I. **Oteseconazole (Vivjoa)** 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 **recurrent vulvovaginal candidiasis (RVVC)** when the following are met:
 1. Member has a history of three or more acute vulvovaginal candidiasis (VVC) episodes within the last 12 months; **AND**
 2. Member is currently experiencing signs and symptoms consistent with an acute episode of VVC (e.g., vulvovaginal pain, pruritis or irritation, abnormal vaginal discharge, etc.); **AND**
 3. Diagnosis of acute VVC has been confirmed by positive KOH or culture; **AND**
 4. Member is of non-reproductive potential, defined as one of the following:
 - i. Postmenopausal; **OR**
 - ii. Member has undergone surgical sterilization (e.g., history of tubal ligation, bilateral salpingo-oophorectomy, or hysterectomy); **OR**
 - iii. Other means of permanent infertility (documentation is verified by a clinical pharmacist at the health plan); **AND**
 5. Member has been treated with weekly oral fluconazole for a period of 6 months; **OR**
 - i. Treatment with fluconazole is not tolerated or contraindicated; **OR**
 - ii. Antifungal susceptibility testing has been conducted and confirms fluconazole resistance; **OR**
 - iii. Member has experienced a recurrence during or following maintenance therapy with fluconazole

- II. Oteseconazole (Vivjoa) is considered investigational when used for all other conditions, including but not limited to:
- A. Acute vulvovaginal candidiasis
 - B. Onychomycosis or other nail fungal infections
 - C. Tinea pedis
 - D. Systemic fungal infections

Renewal Evaluation

- I. See initial evaluation

Supporting Evidence

- I. Oteseconazole (Vivjoa) is an oral azole antifungal that has been FDA-approved to reduce the incidence of recurrent vulvovaginal candidiasis (RVVC). Oteseconazole (Vivjoa) was studied in three Phase 3, randomized, double-blind, placebo-controlled pivotal trials: two VIOLET studies and one ultraVIOLET study. The trial population consisted of a total of 875 post-menarchal females aged 12 years and older who had a diagnosis of RVVC, defined as at least three prior episodes of acute VVC in the past 12 months.
- II. The VIOLET trials consisted of an induction phase with fluconazole 150mg on days one, four, and seven. On day 14 participants were assessed for infection clearance; only participants who had cleared their initial infection were then randomized to receive oteseconazole (Vivjoa) or placebo for the maintenance period. The dosing of oteseconazole (Vivjoa) during the maintenance period was 150mg once daily for one week, followed by 150mg weekly for 11 weeks. The primary efficacy endpoint for both VIOLET trials was the proportion of patients with one or more culture verified acute VVC episodes during the maintenance phase of the study.
- III. In ultraVIOLET, participants were randomized prior to the induction phase to receive oteseconazole (Vivjoa) or fluconazole/placebo. In the oteseconazole (Vivjoa) group, participants received 600mg on day one and 450mg on day two for induction therapy, then oteseconazole (Vivjoa) weekly for 11 weeks starting on day 14 for maintenance therapy. In the fluconazole/placebo group, participants received fluconazole 150mg on days one, four, and seven for induction therapy, then placebo weekly for 11 weeks starting on day 14 for maintenance therapy. Results below:

	Trial 1 (VIOLET)		Trial 2 (VIOLET)		Trial 3 (ultraVIOLET)	
	OTE N = 217	PBO N = 109	OTE N = 218	PBO N = 108	OTE N = 218	FLU/PBO N = 108
Induction regimen	FLU		FLU		OTE	FLU
Maintenance regimen	OTE 150mg QD x7 days, then QW x11 weeks	PBO	OTE 150mg QD x7 days, then QW x11 weeks	PBO	OTE 150mg QW x11 weeks	PBO
Proportion of patients with ≥1 culture-verified acute VVC episode (Day 1 – week 48)*	6.7%	42.8%	3.9%	39.4%	10.3%	42.9%
Proportion of patients with ≥1 culture-verified	27.3%	50.8%	21.3%	49.7%	43.5%	59.0%

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acute VVC episode or received VVC medication (Day 1 – week 48)*						
FLU = fluconazole 150mg on days 1, 4, and 7; PBO = matching placebo; OTE = oteseconazole *All results were statistically significant in favor of oteseconazole						

- IV. Although the trial was designed to allow providers to treat participants with fluconazole for episodes of recurrence, other VVC medications were used during the trial to treat suspected acute VVC infections. The investigators did not initially consider all instances where participants used other VVC medications as incidence of recurrence. A post-hoc sensitivity analysis conducted by the FDA considered the use of other VVC medications as recurrence shows a slightly different efficacy profile, and results are reported in the second endpoint in the table above. Although the post-hoc analysis cannot formally be considered for statistical significance, this shows a more realistic efficacy profile that remains clinically meaningful.
- V. The most commonly reported adverse events consisting of headache (7.4%) and nausea (3.6%). Although the clinical trials included participants who were of reproductive potential, oteseconazole (Vivjoa) is contraindicated in females of reproductive potential and in pregnant and lactating women due to embryo-fetal toxicity risks, including ocular abnormalities based on data from animal trials, that cannot be adequately mitigated given the drug exposure window of approximately 690 days.
- VI. The FDA label defines ‘non-reproductive potential’ as follows: persons who are biological females who are postmenopausal or have another reason for permanent infertility (e.g., tubal ligation, hysterectomy, salpingo-oophorectomy). Although contraception is highly effective at preventing pregnancy, there is always a chance of contraceptive failure with any contraceptive method. Additionally, because the effects of contraception are reversible, use of various contraceptive methods, including abstinence, are not considered ‘permanent infertility’.
- VII. Although the pivotal clinical trials enrolled post-menarchal patients aged 12 years and older, the majority of participants were between age 18 and 34 years and only two total patients under age 18 years participated. Due to the small population size, the true safety and efficacy profile of oteseconazole (Vivjoa) has not been established in patients under the age of 18 years.
- VIII. Clinical guidelines, including those published by the Centers for Disease Control and Prevention (CDC) and Infectious Disease Society of America (IDSA), indicate that diagnosis of VVC can typically be made via the presentation of infection signs/symptoms: pruritis, irritation, vaginal soreness, external dysuria, and dyspareunia accompanied by signs of vulvar edema, erythema, excoriation, fissures and white, thick, curd-like vaginal discharge. For complicated VVC and RVVC, diagnosis should be confirmed with a wet-mount preparation with use of saline and 10% potassium hydroxide (KOH). If KOH is negative, a culture for *Candida* should be obtained.
- IX. RVVC is usually defined as having at least three episodes of acute VVC within one year and are typically caused by azole-susceptible *C. albicans*. Clinical guidelines recommend beginning treatment with induction therapy with a 10-to-14-day course of a topical azole or oral fluconazole, followed by maintenance therapy with fluconazole 150mg once weekly for six months. If oral fluconazole is not feasible, topical clotrimazole (200mg cream twice weekly or 500mg vaginal suppository once weekly) or other intermittent oral or topical antifungal treatment is recommended. After cessation of maintenance therapy, IDSA approximates a 40-50% recurrence rate. Oteseconazole (Vivjoa) may be considered medically necessary if oral fluconazole has been not tolerated, is contraindicated, fluconazole resistance is confirmed, or if

members experience recurrence of acute VVC symptoms anytime during or after maintenance therapy with fluconazole.

- X. According to results of an extension trial reported by the manufacturer, 85% of participants who completed the maintenance regimen with oteseconazole (Vivjoa) did not experience a recurrent episode for up to 96 weeks (approximately two years). However, rates of recurrence beyond two years or safety and efficacy of retreatment with oteseconazole (Vivjoa) has not been established. Due to lack of adequate safety and efficacy data to establish an appropriate timeline for retreatment, renewal requests will be evaluated against initial policy criteria.

Investigational or Not Medically Necessary Uses

- I. Oteseconazole (Vivjoa) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
- A. Acute vulvovaginal candidiasis
 - i. One Phase 2, randomized, double-blind, active-controlled, parallel-group, dose-ranging trial evaluated oteseconazole (Vivjoa) at various doses (300mg once daily, 600mg daily or 600mg twice daily) for three days against a single dose of fluconazole 150mg in the setting of acute VVC. The primary endpoint was the proportion of participants with therapeutic cure at the test-of-care (TOC) day 28 visit. This study was not appropriately powered for statistical analysis and statistical significance could not be evaluated. However, the nominal data indicate that no difference in therapeutic cure was identified between any of the oteseconazole (Vivjoa) groups and the fluconazole group.
 - B. Onychomycosis or other nail fungal infections
 - C. Tinea pedis
 - D. Systemic fungal infections

References

1. Brand SR, Sobel JD, Nyirjesy P, et al. A Randomized Phase 2 Study of VT-1161 for the Treatment of Acute Vulvovaginal Candidiasis. *Clinical Infectious Diseases*. 2021;73(7):e1518-24.
2. Sobel JD, Nyirjesy P. Oteseconazole: an advance in treatment of recurrent vulvovaginal candidiasis. *Future Microbiol.* (2021) 16(18), 1453-1461.
3. New Drug Review: oteseconazole (Vivjoa). IPD Analytics. May 2022.
4. Centers for Disease Control and Prevention (CDC). 2015 Sexually Transmitted Diseases Treatment Guideline: Vulvovaginal candidiasis. Accessed July 19, 2021.
5. Pappas PG, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. *Clinical Infectious Diseases*. 2016;62(4):e1-50.
6. Vivjoa [Prescribing Information]. Mycovia Pharmaceuticals: Durham, NC. April 2022.
7. Kotch LE. Integrated Review - Application number: 211288Orig1s000. Center for Drug Evaluation and Research. August 26, 2021.

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated wording to reflect standard policy language; Added criteria for fluconazole resistance	03/2023
Policy created	08/2022

Policy Type: PA

Pharmacy Coverage Policy: UMP206

Description

Oxymetazoline (Upneeq) is an alpha-adrenergic receptor agonist ophthalmic solution.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
oxymetazoline (Upneeq)	0.1% solution dropperette	aponeurotic acquired blepharoptosis	30 dropperettes/30 days

Initial Evaluation

- I. Oxymetazoline (Upneeq) 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 ophthalmologist; **AND**
 - C. A diagnosis of **aponeurotic acquired blepharoptosis** (i.e., not being used in mechanical blepharoptosis, Horner syndrome, myasthenia gravis) when the following are met:
 1. Provider attestation of **ALL** of the following:
 - i. Member has functional impairment in activities of daily living due to blepharoptosis; **AND**
 - ii. The *superior* visual field is less than 20 degrees when untaped; **AND**
 - iii. There is at least a 20-degree improvement when taped; **AND**
 - iv. There is a marginal reflex distance (MRD)-1 of 2.0 mm or less
- II. Oxymetazoline (Upneeq) is considered investigational when used for all other conditions, including but not limited to:
 - A. Non aponeurotic blepharoptosis

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**

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- III. Provider attestation indicating member has exhibited improvements in points seen in visual field test

Supporting Evidence

- I. Blepharoptosis, also known as ptosis, is a unilateral or bilateral dropping of the upper eyelid due to a congenital or acquired abnormality of the muscles that elevate the eyelid. Acquired blepharoptosis may be due different causes such as aponeurotic (usually age related), mechanical (e.g., eyelid mass), neurologic (e.g., Horner syndrome, myasthenia gravis), and myogenic (e.g., systemic muscular dysfunctions). Aponeurotic is the most common and is associated with aging. Surgery is the standard of care for patients who develop an obscured visual field due to ptosis and can also be considered for cosmetic purposes. However, surgery comes with known risks (e.g., failure of the eye to close completely, infection, edema, under correction/overcorrection, eyelid asymmetry, granuloma formation, and corneal foreign body sensation). Oxymetazoline (Upneeq) is an alternative to surgery in those who are not suitable candidates or those seeking a less costly, non-surgical option.
- II. Oxymetazoline (Upneeq) was studied in two phase 3, double masked, randomized, vehicle-controlled trials in patients with acquired blepharoptosis. The primary endpoint was a change in the number of points seen in the top 4 rows of the Leicester Peripheral Field Test (LPFT) on treatment day 1 and 14. Patients included in trial 202 had a mean marginal reflex distance (MRD-1) of 1.04 ± 0.74 mm (Upneeq) and 1.07 ± 0.70 mm (vehicle) at baseline.

Endpoints	RVL-1201-201 (n=140)		RVL-1201-202 (n=164)	
	Upneeq	Vehicle	Upneeq	Vehicle
	n=94	n=46	n=109	n=55
Mean change in LPFT Day 1 (6 hours post instillation)	5.2 points	1.5 points	6.3 points	2.1 points
	Mean difference: 3.7 [1.8, 5.6] P<0.01		Mean difference: 4.2 [2.4, 6.1] P<0.01	
Mean change in LPFT Day 14 (2 hours post instillation)	6.4 points	2.2 points	7.7 points	2.4 points
	Mean difference: 4.2 [2.0, 6.0] P<0.01		Mean difference: 5.3 [3.7, 7.1] P<0.01	
Mean change in MRD-1 from baseline (highest change; day 14, 2 hours post-instillation)	MRD-1 endpoints not published		1.3 mm	0.4 mm
			P < 0.05	

- III. Although oxymetazoline (Upneeq) showed a statistically significant improvement relative to vehicle for improving LPFT, the quality of the evidence is considered low as LPFT is a modified version of Humphrey visual field test that is not typically used in practice, coupled with limited information available on trial data, unknown components used as the vehicle product, and unknown safety with use over 42 days.
- IV. Clinical trials noted above excluded certain acquired causes of blepharoptosis (i.e., mechanical, Horner syndrome, myasthenia gravis). Efficacy of oxymetazoline (Upneeq) outside of the aponeurotic acquired blepharoptosis population is unknown.
- V. FDA approval of oxymetazoline (Upneeq) is specific to the adult population only. Although one of the clinical trials included patients 9 years and older, the youngest patient that received oxymetazoline (Upneeq) in that trial was 20 years old. Thus, safety and efficacy of oxymetazoline (Upneeq) has not been established in pediatric patients.

Investigational or Not Medically Necessary Uses

- I. Oxymetazoline (Upneeq) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Non aponeurotic blepharoptosis

References

1. Upneeq [Prescribing Information]. RVL Pharmaceuticals, Inc.: Bridgewater, NJ. August 2020.
2. Korenfeld M, Kannarr S, Silverstein S, et. al. Effect of oxymetazoline on blepharoptosis: results of a phase 3 randomized, double masked, placebo-controlled study – Poster Presentation Presented at the American Academy of Optometry (AAO) Meeting – October 2019.
3. RVL Pharmaceuticals, Inc. Study of the Safety and Efficacy of RVL-1201 in the Treatment of Acquired Blepharoptosis. Available from <https://clinicaltrials.gov/ct2/show/NCT02436759>. NLM identifier: NCT02436759
4. UpToDate, Inc. Overview of ptosis. UpToDate [database online]. Waltham, MA. Last updated May 06, 2020. Available at: <http://www.uptodate.com/home/index.html>.
5. Alsuhaibani A. et al. Blepharoptosis. American Academy of Ophthalmology EyeWiki website. Last updated July 25, 2020. Available at: <https://eyewiki.org/Blepharoptosis#Disease>.
6. Santen and RVL Pharmaceuticals, Inc., an Osmotica Company, enter into an exclusive license agreement in Japan, Asia, and EMEA for rvl-1201, a first-in-class treatment for acquired blepharoptosis [Press Release]. Osmotica Pharmaceuticals. <https://ir.osmotica.com/news-releases/news-release-details/santen-and-rvl-pharmaceuticals-inc-osmotica-company-enter>. Published July 28, 2020.
7. Osmotica Pharmaceuticals plc receives FDA approval for Upneeq™ (oxymetazoline hydrochloride ophthalmic solution), 0.1% for acquired blepharoptosis (droopy eyelid) in adults [Press Release]. GlobeNewswire. <https://www.globenewswire.com/news-release/2020/07/09/2059809/0/en/Osmotica-Pharmaceuticals-plc-Receives-FDA-Approval-for-Upneeq-oxymetazoline-hydrochloride-ophthalmic-solution-0-1-for-Acquired-Blepharoptosis-Droopy-Eyelid-in-Adults.html>. Published July 9, 2020
8. Kansteiner F. Osmotica bucks pandemic trend with in-person sales calls for eye drug launch [Press Release]. Fierce Pharma. <https://www.fiercepharma.com/marketing/osmotica-nets-approval-for-first-class-droopy-eyelid-med>. Published July 13, 2020.
9. Prioritized List of Health Services. Oregon Health Authority. August 14, 2020. Available at: <https://www.oregon.gov/oha/hpa/dsi-herc/pages/prioritized-list.aspx> 2020 Prioritized List of Health Services.pdf.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	11/2020

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP256

Split Fill Management*

Description

Pacritinib (Vonjo) is a Janus associated kinase 2 (JAK2) inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
pacritinib (Vonjo)	Intermediate- or high-risk myelofibrosis with severe thrombocytopenia (platelet count below $50 \times 10^9/L$)	100 mg capsules	120 capsules/30 days

Initial Evaluation

- I. **Pacritinib (Vonjo)** 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. A diagnosis of **intermediate- or high-risk myelofibrosis** when the following are met:
 1. Splenomegaly is present and spleen volume is documented; **AND**
 2. Member has severe thrombocytopenia (defined as platelet count below $50 \times 10^9/L$); **AND**
 3. Documentation of disease-related symptoms (e.g., fatigue, shortness of breath, bruising, bleeding, fever, bone pain)
- II. Pacritinib (Vonjo) is considered not medically necessary when criteria above are not met and/or when used for:
 - A. Myelofibrosis without severe thrombocytopenia (i.e., platelet count is $\geq 50 \times 10^9/L$)
- III. Pacritinib (Vonjo) is considered investigational when used for all other conditions, including but not limited to:
 - A. Low risk myelofibrosis
 - B. Polycythemia vera
 - C. Graft versus host disease
 - D. Lymphoproliferative neoplasms
 - E. Solid tumors (e.g., prostate, colorectal, lung)

- F. Acute myeloid leukemia (AML)
- G. Chronic lymphocytic leukemia, small lymphocytic lymphoma
- H. COVID-19

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 intermediate- or high-risk myelofibrosis (has not transformed to AML); **AND**
- IV. Member has exhibited improvement in or stability of spleen volume; **AND**
- V. Member has exhibited improvement in or stability of disease-related symptoms (e.g., fatigue, shortness of breath, bruising, bleeding, fever, bone pain).

Supporting Evidence

- I. Myelofibrosis (MF) is a cancer of the bone marrow. Symptoms are non-specific (e.g., fatigue, shortness of breath, bleeding) and splenomegaly is common. Over time MF may progress to acute myeloid leukemia (AML). There are five risk levels of disease that correlate with prognosis, and treatment is based on risk. When patients are not eligible for allogeneic stem cell transplant, symptom targeted therapy may be used in those with intermediate or higher risk MF. Symptomatic therapies include hydroxyurea and JAK inhibitors: ruxolitinib (Jakafi), fedratinib (Inrebic), pacritinib (Vonjo). JAK inhibitors have only been sufficiently evaluated in patients with at least intermediate-risk MF and have unknown clinical value for lower risk disease. JAK inhibitors do not reverse fibrosis or prolong survival but may reduce spleen size and improve disease-related symptoms. In absence of splenomegaly and symptoms, these medications have unknown application. Given the specialized diagnosis, treatment, and monitoring, prescribing by or in consultation with a specialist is required.
- II. Ruxolitinib (Jakafi) and fedratinib (Inrebic) are approved for MF in those with a platelet count $\geq 50 \times 10^9/L$. These medications are known to cause thrombocytopenia and are recommended to be discontinued if the platelet count drops below $50 \times 10^9/L$. Pacritinib (Vonjo), has a unique approval, and was approved under the accelerated approval pathway based on spleen volume reduction (SVR) when platelet count is under $50 \times 10^9/L$ (severe thrombocytopenia). Pacritinib (Vonjo) has been evaluated in adults; use in pediatrics or adolescents has unknown value or consequences. Outside of a clinical trial setting, therapy should only be utilized in adults.
- III. Pacritinib (Vonjo) was evaluated in two Phase 3 trials, PERSIST1 and PERSIST2. The accelerated approval was based on results from PERSIST2, a randomized, open-label trial vs. best available therapy (BAT) (included 39% of patients on ruxolitinib [Jakafi]) for 24 weeks (n=311). Patients had platelets $< 100 \times 10^9/L$ (45% had $< 50 \times 10^9/L$). Regimens of 400 mg once daily and 200 mg twice daily were evaluated. Outcomes included spleen volume reduction (SVR) of $\geq 35\%$, and daily symptom score reduction of at least 50% via the MPN-SAF TSS tool. The trial indicated a

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statistically significant improvement in SVR for both treatment arms compared to BAT, and the 200 mg twice daily arm showed an improvement in daily symptoms scores over BAT. Subgroup analyses for the specific FDA-approved population (i.e., platelet count $<50 \times 10^9/L$) were not statistically evaluated. PERSIST1 was a randomized, open-label trial evaluating 400 mg once daily vs. BAT for 24 weeks (n=327). For pacritinib (Vonjo), 148 patients (67%) had platelets $> 100 \times 10^9/L$, 37 (17%) had $< 100 \times 10^9/L$, and 35 (16%) had $< 50 \times 10^9/L$. There was statistical significance over BAT for SVR $\geq 35\%$, and reduction in TSS $\geq 50\%$.

- IV. There is positive evidence to indicate clinical value of pacritinib (Vonjo) in patients with MF with severe thrombocytopenia; however, given lack of clinical trials focused solely on this specific population, as well as other trials with various doses and conflicting results, the FDA has granted accelerated approval based on SVR, and continued approval is contingent upon verification of clinical benefit in the PACIFICA3 Phase 3 clinical trial. Results are due in 2025. Of note, this therapy is only FDA approved given the already seen impact on SVR and a condition of the accelerated approval, is that the manufacturer confirms that SVR and this therapy leads to a clinical benefit. Until confidence in the clinical benefit is determined, therapy is reserved for those that have reduction in spleen volume and also experience symptom improvement.
- V. Given the limited approval of pacritinib (Vonjo), coverage consideration is limited to MF with severe thrombocytopenia and disease-related symptoms. There is unknown clinical value in those without symptoms. Coverage consideration is also limited to those with severe thrombocytopenia as other treatment options with full FDA-approval, stronger evidence for efficacy, and more developed safety profiles are available; ruxolitinib (Jakafi) and fedratinib (Inrebic). Pacritinib (Vonjo) has some evidence for efficacy in patients that have platelet counts above $50 \times 10^9/L$ and could be considered as a treatment option for patients with trial and failure or contraindication to ruxolitinib (Jakafi) and fedratinib (Inrebic); however, when possible, therapy should be reserved for the FDA-approved population as the efficacy and safety profile of pacritinib (Vonjo) continues to develop. In 2016 the FDA put a hold on the trials due to noted deaths from hemorrhage, cardiac failure and arrest. The hold was later lifted in 2017 after evaluation of all clinical trial evidence; however, the safety profile of pacritinib (Vonjo) is not fully understood. One unique black box warning for fedratinib (Inrebic) is encephalopathy, and in those that experience signs/symptoms or are at an increased risk may not be appropriate for fedratinib (Inrebic) use. This has not yet been noted for pacritinib (Vonjo) or ruxolitinib (Jakafi); however, comparative safety and efficacy data for these therapies are not available.
- VI. Pacritinib (Vonjo) outcomes of SVR and improvement in daily symptoms were evaluated by week 24; a six-month initial approval is granted to allow sufficient time for and evaluation of symptom response. There is lack of strong evidence to indicate treatment response will occur if not reached by this time. Pacritinib (Vonjo) has shown clinical value in reducing spleen size and improving disease-related symptoms; thus, continuation of therapy is reasonable when both of these are stable or have improved. Reduction in spleen size without improvement in disease-related symptoms has unknown clinical value at this time. Of note, spleen volume or size may be assessed or examined by physical examination (i.e., palpation); however, if the spleen is not palpable, imaging is appropriate for determining spleen size or volume. This is done when there is a need to determine the spleen size or changes when physical examination is insufficient (e.g., for determining response to therapy).

Investigational or Not Medically Necessary Uses

- I. Pacritinib (Vonjo) is considered not medically necessary in patients with MF with platelet counts greater than $50 \times 10^9/L$ when patients are eligible for the two JAK inhibitors that are FDA-approved in that population; ruxolitinib (Jakafi) and fedratinib (Inrebic). Ruxolitinib (Jakafi) and fedratinib (Inrebic) have established safety and efficacy profiles for patients with platelets greater than $50 \times 10^9/L$. In the event of treatment failure or contraindication to these two JAK inhibitors, pacritinib (Vonjo) could be considered a fair treatment option; however, when patients do not have failure or contraindication to ruxolitinib (Jakafi) and fedratinib (Inrebic), use of pacritinib (Vonjo) should be reserved for patients with severe thrombocytopenia.
- II. Pacritinib (Vonjo) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Low risk myelofibrosis
 - B. Polycythemia vera
 - C. Graft vs. host disease
 - D. Lymphoproliferative neoplasms
 - E. Solid tumors (e.g., prostate, colorectal, lung)
 - F. Acute myeloid leukemia (AML)
 - G. Chronic lymphocytic leukemia, small lymphocytic lymphoma
 - H. COVID-19

** 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. Mesa RA, Vannucchi AM, Mead A, et al. Pacritinib versus best available therapy for the treatment of myelofibrosis irrespective of baseline cytopenias (PERSIST-1): an international, randomised, phase 3 trial. *Lancet Haematol*. 2017;4(5):e225-e236.
2. Mascarenhas J, Hoffman R, Talpaz M, et al. Pacritinib vs best available therapy, including ruxolitinib, in patients with myelofibrosis. A randomized clinical trial. *JAMA Oncol*. 2018;4(5):652-659.
3. Vonjo [Prescribing Information]. CTI Biopharma Corp. Seattle, WA. February 2022.
4. National Comprehensive Cancer Network. NCCN Guidelines: Myeloproliferative Neoplasms. V1.2022, updated 02/28/2022.
5. Jakafi [Prescribing Information]. Incyte Corporation. Wilmington, DE. September 2021.
6. Inrebic [Prescribing Information]. Celgene Corporation. Summit, NJ. August 2019.

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.

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Policy Name	Disease state
ruxolitinib (Jakafi, Opzelura) Policy	Intermediate or high-risk myelofibrosis
fedratinib (Inrebic) Policy	Myelofibrosis

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	05/2022

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP051

Description

Palivizumab (Synagis) is a humanized monoclonal antibody directed against the fusion protein of respiratory syncytial virus (RSV).

Length of Authorization

- Initial: Five months
- Renewal: N/A

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
palivizumab (Synagis)	100 mg/1mL	Respiratory syncytial virus (RSV) prophylaxis	15 mg/kg (1 dose) per 28 days
	50 mg/0.5mL		

Initial Evaluation

- I. Palivizumab (Synagis) may be considered medically necessary when the following criteria below are met:
 - A. Therapy is given during the current RSV season; **AND**
 - B. Member is being managed by, or in consultation with, a pulmonologist or cardiologist; **AND**
 - C. A diagnosis of one of the following:
 1. **Preterm Infants WITHOUT congenital morbidities** (e.g. chronic lung disease of prematurity; or congenital heart disease); **AND**
 - i. Member was born before 29 weeks, 0 days of gestation; **AND**
 - ii. Member is less than 12 months of postnatal age; **OR**
 2. **Preterm Infants WITH Chronic Lung Disease (CLD)**; **AND**
 - i. Member was born before 32 weeks, 0 days of gestation; **AND**
 - ii. Member required respiratory support (supplement with greater than 21% oxygen) for at least the first 28 days after birth; **AND**
 - iii. Member is less than 12 months of age; **OR**
 - iv. Member is less than 24 months of age; **AND**
 - v. Continues to require medical support (e.g., chronic corticosteroid therapy, diuretic therapy, or supplemental oxygen) during the 6-month period before the start of second RSV season; **OR**
 3. **Infants and Children with Hemodynamically Significant Congenital Heart Disease (CHD)**; **AND**
 - i. Member is less than 12 months of age; **AND**
 - ii. Member has moderate to severe pulmonary hypertension; **OR**
 - iii. Member has cyanotic heart disease; **OR**

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- iv. Member has acyanotic heart disease; **AND**
 - a. Member is receiving medication to control congestive heart failure; **AND**
 - b. Member will require cardiac surgical procedures; **OR**
- 4. **Children undergoing cardiac transplantation during RSV season; AND**
 - i. Member is less than 24 months of age; **OR**
- 5. **Infants with Anatomic Pulmonary Abnormalities or Neuromuscular disorder; AND**
 - i. Member is less than 12 months of age; **AND**
 - ii. Member has an impaired ability to clear secretions from the upper airway; **OR**
- 6. **Immunocompromised Children; AND**
 - i. Member is less than 24 months of age; **AND**
 - ii. Member is profoundly immunocompromised (e.g. undergoing chemotherapy, HIV, SCID, DiGeorge, IgA deficiency, Hypergammaglobulinemia etc.); **OR**
- 7. **Children with Cystic Fibrosis, Primary Ciliary Dyskinesia, or other rare lung disease; AND**
 - i. Member is less than 12 months of age; **AND**
 - a. Member has clinical evidence of chronic lung disease (CLD); **OR**
 - b. Member has clinical evidence of nutritional compromise; **OR**
 - ii. Member is less than 24 months of age; **AND**
 - a. Member had a hospitalization for pulmonary exacerbation in the first year of life; **OR**
 - b. Member has abnormalities on chest radiography/chest computed tomography that persist when stable; **OR**
 - c. Member has a weight for length less than the 10th percentile

II. Palivizumab (Synagis) is considered not medically necessary when criteria above are not met and/or when used for:

- A. Infants or children who were born after 32 weeks
- B. Infants and children with hemodynamically insignificant heart disease such as:
 - 1. Secundum atrial septal defect
 - 2. Small ventricular septal defect
 - 3. Pulmonic stenosis
 - 4. Uncomplicated aortic stenosis
 - 5. Mild coarctation of the aorta
 - 6. Patent ductus arteriosus
- C. Infants with lesions adequately corrected by surgery, unless they continue to require medication for congestive heart failure
- D. Infants with mild cardiomyopathy who are not receiving medical therapy for the condition
- E. Children in the second year (≥ 24 months) of life
- F. Children with Down syndrome without other comorbid conditions listed in the Initial Evaluation (section I) portion of this policy.

- III. Palivizumab (Synagis) is considered investigational when used for all other conditions, including but not limited to:
- A. For the treatment of RSV

Supporting Evidence

- I. For current RSV trends, refer to: <http://www.cdc.gov/surveillance/nrevss/rsv/index.html>. The CDC utilizes the past year's surveillance season data to predict the timing of the next year's outbreak.
- II. Palivizumab (Synagis) is a respiratory syncytial virus (RSV) F protein inhibitor monoclonal antibody indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus (RSV) in pediatric patients. The FDA approved palivizumab (Synagis) in 1998 for pediatric patients with a history of premature birth (<35 weeks of gestation), children with bronchopulmonary dysplasia (BPD), and those with hemodynamically significant congenital heart disease (CHD).
- III. The American Academy of Pediatrics (AAP) committee on infectious diseases (COID) has undertaken a systematic review of all recent, and older, peer-reviewed literature relating to the burden of respiratory syncytial virus (RSV) disease in infants and children, specifically focusing on publications that delineate children at greatest risk of serious RSV disease and studies that define pharmacokinetics, safety, and efficacy. Detailed input regarding this guidance has been solicited from 21 committees, councils, sections, and advisory groups within the AAP, as well as organizations outside the AAP. The updated (reviewed every 3 years) recommendations by AAP are based on review of the quality of all available data, as well as real world clinical impact of palivizumab (Synagis) prophylaxis for the population subset in the United States.
- IV. Available clinical data and the AAP recommendations note that there is limited clinical benefit derived from palivizumab prophylaxis for otherwise healthy infants and children and therefore, should be limited to the patient population described in this policy. Furthermore, the package insert for palivizumab (Synagis) states: "Synagis is indicated for the prevention of serious lower respiratory tract disease caused by RSV in children at high risk of RSV disease." And in the absence of a specific definition of "high risk" by the US FDA, the AAP has provided guidance for determining the "high risk" population characteristics which have been used to create this policy.
- V. Palivizumab (Synagis) was evaluated in two randomized, double-blind, placebo-controlled trials of prophylaxis against RSV infection in children at high risk of an RSV-related hospitalization.
 - Trial 1 was conducted during a single RSV season with 1502 children who were less than or equal to 24 months of age with bronchopulmonary dysplasia (BPD) or infants with premature birth (less than or equal to 36 weeks of gestation) who were less than or equal to 6 months of age at study entry.
 - i. Results of Trial 1: 4.8% (49/1002) participants were hospitalized in the palivizumab (Synagis) group compared to 10.6% (52/500) participants were hospitalized in the placebo group.

- Trial 2 was conducted over four consecutive RSV seasons with 1287 children less than or equal to 24 months of age with hemodynamically significant congenital heart disease.
 - i. Results of Trial 2: 5.3% (34/639) participants were hospitalized in the palivizumab (Synagis) group compared to 9.7% (63/648) participants were hospitalized in the placebo group.
- VI. A technical review by the American Academy of Pediatrics (AAP) was completed in 2014 and the recommendation was palivizumab (Synagis) for RSV prophylaxis "cannot be considered as high-value health care for any group of infants" because there is minimal benefit, in addition to its high cost. From that technical review, AAP published the following guidance in 2014: Palivizumab (Synagis) Prophylaxis Among Infants and Young Children at Increased Risk of Hospitalization for Respiratory Syncytial Virus Infection.
 - The AAP states available data for infants born at 29 weeks, 0 days' gestation or later do not identify a clear gestational age cutoff for which the benefits of prophylaxis are clear. For this reason, infants born at 29 weeks, 0 days' gestation or later are not universally recommended to receive palivizumab (Synagis) prophylaxis. Infants 29 weeks, 0 days' gestation or later may qualify to receive prophylaxis on the basis of congenital heart disease (CHD), chronic lung disease (CLD), or another condition.
- VII. For preterm infants born before 32 weeks, 0 days of gestational age, palivizumab (Synagis) prophylaxis is recommended if the infant developed chronic lung disease (CLD) of prematurity. This typically involves use of supplemental Oxygen (O₂) therapy during the first 28 days after birth to mitigate hypoxia and cyanosis. While normal O₂ saturation in inspired room air (FiO₂) is 20%, infants with CLD require supplementation with > 21% O₂ concentration. The Oxygen need is determined by the patient's disease severity and can range from 21% to up to 100%. Per WHO recommendations for treatment of CLD, supplemental Oxygen therapy should be initiated with 30% oxygen or air (if blended oxygen is not available), rather than with 100% oxygen. The use of progressively higher concentrations of oxygen should only be considered for newborns undergoing oxygen therapy if their heart rate is less than 60 beats per minute after 30 seconds of adequate ventilation with 30% oxygen or air.
- VIII. AAP guidelines recommend palivizumab (Synagis) for infants with hemodynamically significant CHD. In this setting, the best therapeutic benefit is likely for infants with acyanotic heart disease who are receiving medication to control congestive heart failure and will require cardiac surgical procedures and in infants with moderate to severe pulmonary hypertension. Decisions regarding palivizumab prophylaxis for infants with cyanotic heart defects in the first year of life may be made in consultation with a pediatric cardiologist. According to recommendations from key experts in pediatric cardiology, infants with cyanotic heart defects (e.g. heart valve defects, Ebstein anomaly, hypoplastic left heart syndrome, Tetralogy of Fallot, Truncus arteriosus) are at a much higher risk of complications from RSV as compared to those with acyanotic heart defects (e.g. congenital septal defects, patent ductus arteriosus, pulmonary stenosis, aortic stenosis). Consequently, prophylaxis using palivizumab (Synagis) may have a significant, real world clinical and potentially life-saving impact for the infant population with cyanotic heart disease. AAP guidelines recommend that the decision to use palivizumab (Synagis) in cyanotic heart disease patients must be made by or in consultation with a pediatric cardiologist.
- IX. During the second year of life, consideration of palivizumab prophylaxis is recommended only for infants who satisfy the definition of CLD of prematurity and continue to require medical support (chronic corticosteroid therapy, diuretic therapy, or supplemental oxygen) during the 6-

- month period before the start of the second RSV season. For infants with CLD who do not continue to require medical support in the second year of life prophylaxis is not recommended.
- X. Although the National Perinatal Association 2018 Respiratory Syncytial Virus (RSV) Prevention Clinical Practice Guideline: An Evidence-Based Interdisciplinary Collaboration published additional guidance and new information as it relates to RSV, after reviewing the new information, the AAP still recommended their guidelines from 2014 as the new evidence did not change the cost-benefit analysis that was done.

Investigational or Not Medically Necessary Uses

- I. The listed diagnoses are included in the AAP 2017 RSV Guidance as not medically necessary for immunoprophylaxis with palivizumab (Synagis)
- A. Infants or children who were born after 32 weeks
 - B. Infants and children with hemodynamically insignificant heart disease such as:
 - i. Secundum atrial septal defect
 - ii. Small ventricular septal defect
 - iii. Pulmonic stenosis
 - iv. Uncomplicated aortic stenosis
 - v. Mild coarctation of the aorta
 - vi. Patent ductus arteriosus
 - C. Infants with lesions adequately corrected by surgery, unless they continue to require medication for congestive heart failure
 - D. Infants with mild cardiomyopathy who are not receiving medical therapy for the condition
 - E. Children in the second year (≥ 24 months) of life
 - F. Children with Down syndrome without other comorbid conditions listed in the Initial Evaluation (section I) portion of this policy.
- II. Treatment of RSV
- A. Safety and efficacy has not been established for the use of palivizumab (Synagis) for the treatment of RSV.

References

1. Synagis [Prescribing Information]. Gaithersburg, MD: MedImmune, LLC. March 2014. Wegzyn C, Toh LK, Biguenet S, et al. Safety and Effectiveness of Palivizumab in Children at High Risk of Serious Disease Due to Respiratory Syncytial Virus Infection: A Systematic Review. *Infect Dis Ther*. 2014 Dec; 3(2): 133–158.
2. American Academy of Pediatrics: Updated Guidance for Palivizumab Prophylaxis Among Infants and Young Children at Increased Risk of Hospitalization for Respiratory Syncytial Virus Infection. Available at: <https://pediatrics.aappublications.org/content/134/2/415>
3. American Academy of Pediatrics: RSV recommendations unchanged after review of new data. Available at: <https://www.aappublications.org/news/2017/10/19/RSV101917>
4. Policy Statement: Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. American Academy of Pediatrics Committee on Infectious Diseases; American Academy of Pediatrics Bronchiolitis Guidelines Committee. *Pediatrics*. August 2014; 134(2): e415-20. doi: 10.1542/peds.2014-1665. Reaffirmed February 2019. Available online at <https://pediatrics.aappublications.org/content/134/2/415.full#sec-13>.

5. Goldstein M, Phillips R, DeVincenzo J, et al. The National Perinatal Association 2018 Respiratory Syncytial Virus (RSV) Prevention Clinical Practice Guideline: An Evidence-Based Interdisciplinary Collaboration. October 2017.
6. Center for Disease Control and Prevention: Respiratory Syncytial Virus Infection (RSV). Available at: <https://www.cdc.gov/rsv/clinical/index.html>
7. Red Book® 2018. Committee on Infectious Diseases; American Academy of Pediatrics; David W. Kimberlin, MD, FAAP; Michael T. Brady, MD, FAAP; Mary Anne Jackson, MD, FAAP; Sarah S. Long, MD, FAAP. Section 3: Respiratory Syncytial Virus. Available at <https://redbook.solutions.aap.org/Book.aspx?bookid=2205>. Accessed December 4th, 2020.

Policy Implementation/Update:

Action and Summary of Changes	Date
Formatting edits and minor edits to wording used in efforts to provide more clarity of policy intent; Addition of indication of 'cyanotic heart disease' as per AAP guidelines; Updated Supporting Evidence section to include more information surrounding clinical benefits of palivizumab (Synagis) prophylaxis and clarification that this policy follows AAP recommendations based on quality of clinical evidence instead of FDA approved indications listed in package insert	12/2020
Transitioned criteria into policy with supporting evidence, and incorporated the updated AAP RSV prophylaxis guidelines that details the specific coverage recommendations for: chronic lung disease in patients less than 24 months, patients less than 12 months with hemodynamically significant chronic heart disease, cardiac transplantation in patients less than 24 months, anatomic pulmonary abnormalities/neuromuscular disorder in patients less than 12 months, immunocompromised children, children with rare lung disease. Additionally, incorporated the recommendations from the updated AAP RSV prophylaxis guidelines to detail what diagnoses are not medically necessary for RSV prophylaxis/Synagis.	09/2019

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP317

Description

Palopegteriparatide (Yorvipath) is a subcutaneously administered parathyroid hormone analog prodrug that acts as continuous endogenous parathyroid hormone (1-34) to regulate calcium and phosphate homeostasis.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
palopegteriparatide (Yorvipath)	Hypoparathyroidism	168 mcg/0.56 mL pen	1.12 mL/28 days (2 pens/28 days)
		294 mcg/0.98 mL pen	1.96 mL/28 days (2 pens/28 days)
		420 mcg/1.40 mL pen	2.80 mL/28 days (2 pens/28 days)

Initial Evaluation

- I. **Palopegteriparatide (Yorvipath)** 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 endocrinologist or nephrologist; **AND**
 - C. A diagnosis of **hypoparathyroidism** when the following are met:
 1. The disease is present for at least 6 months; **AND**
 2. Provider attestation of normal serum vitamin D levels at baseline; **AND**
 3. Provider attestation of inappropriately low serum parathyroid hormone (PTH) levels; **AND**
 4. History of persistent hypocalcemia and a current calcium level of:
 - i. Albumin-adjusted serum calcium level of 7.8 mg/dL or greater; **OR**
 - ii. Ionized serum calcium level of 4.4 mg/dL or greater; **AND**
 5. The member does not have acute post-surgical hypoparathyroidism; **AND**
 - D. Documentation that the member has not achieved disease control with conventional therapies of vitamin D (active: 0.25-3µg/day of calcitriol; analog: 1,000-100,000 IU per day of cholecalciferol [D3]; 50,000 IU weekly to daily of ergocalciferol [D2]) and therapeutic doses of elemental calcium (>600mg/day); **AND**
 1. The member will continue conventional therapies (active or analog vitamin D and oral calcium) in combination with palopegteriparatide (Yorvipath) unless they are contraindicated or not tolerated.

- II. Palopegteriparatide (Yorvipath) is considered investigational when used for all other conditions, including but not limited to:
 - A. Osteoporosis
 - B. Acute post-surgical hypoparathyroidism

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., decrease weakness or fatigue, reduction of muscle aches or cramps] **AND**
- IV. Documentation of improved albumin-corrected or ionized serum calcium into the normal reference range (albumin-corrected: 8.5 – 10.5 mg/dL; ionized serum: 4.5 – 5.6 mg/dL); **AND**
- V. The member no longer requires active or analog vitamin D or therapeutic doses of elemental calcium; **OR**
 - A. The member has shown significant reduction in doses of conventional therapy (active or analog vitamin D and oral calcium); **OR**
 - B. The member is still titrating palopegteriparatide (Yorvipath).

Supporting Evidence

- I. Palopegteriparatide (Yorvipath) was approved based on a Phase 3, randomized, double-blind, placebo-controlled (PaTHway) trial in adult patients with confirmed chronic hypoparathyroidism who were treated with conventional therapy (CT, oral calcium supplementation and active or analog vitamin D products). Patients received either palopegteriparatide (Yorvipath) or placebo while continuing CT. The starting dose of palopegteriparatide (Yorvipath) was 18 mcg once daily and titrated to an optimal dose per protocol. The primary outcome was assessed at week 26 with a composite endpoint of proportion of participants who achieved albumin-adjusted serum calcium in the normal range, independence from active vitamin D and therapeutic doses of elemental calcium, and no dose increases of study drug during the 4 weeks leading up to week 26. Secondary outcomes included measurement of routine laboratory values and patient reported outcomes (PRO) included the hypoparathyroidism patient experience scale (HPES) and short form 36 (SF-36) that evaluated quality of life and physical functioning at baseline and week 26.
- II. A key inclusion criterion of the PaTHway clinical trial required participants to be 18 years of age or older. The study did not contain any patients younger than 18 years and the safety and efficacy in the pediatric and adolescent population is unknown.
- III. A key inclusion criteria of the PaTHway clinical trial was an albumin-adjusted (≥ 7.8 mg/dL) or ionized (≥ 4.4 mg/dL) serum calcium within normal or slightly below normal range. Treatment in members below these cutoffs is not clinically appropriate due to being classified as having severe hypocalcemia. The safety and efficacy of palopegteriparatide (Yorvipath) has not been established in this patient population is considered a limitation for use, as the product

information titration scheme was only evaluated in adults who first achieved albumin-corrected serum calcium of at least 7.8mg/dL using calcium and active vitamin D treatment.

- IV. Treatment with palopegteriparatide (Yorvipath) was found to be statistically significant ($p<0.0001$) in meeting the composite endpoint at week 26 versus placebo with 48 (79%) patients in the treatment group meeting all the components of the composite endpoint against one (5%) patient in the placebo group. The PRO HPES and SF-36 showed improvement in all domains of each scale at week 26 as compared to baseline.
- V. The 52-week open label extension (OLE) results showed that the primary composite endpoint was met in 81% of total participants. There was a modest percent increase of participants that met the primary endpoint but supports the ongoing durability and effect of this treatment.
- VI. Injection site reactions (31% vs. 0), hypercalcemia (10% vs. 0%), and headache (21% vs. 10%) were the most reported adverse events for palopegteriparatide (Yorvipath) and placebo, respectively at week 26. There was one reported death across both groups in which a patient in the palopegteriparatide (Yorvipath) arm with multiple cardiovascular risk factors including hypertension, hyperlipidemia, and obesity who suffered a fatal cardiac arrest, but was not deemed related to the drug. There are no specific contraindications; however, warning and precautions include: hypercalcemia, hypocalcemia, unintended serum calcium changes, orthostatic hypotension, and potential risk of osteosarcoma.
- VII. The 2022 Summary Statement and Guidelines for the Evaluation and Management of Hypoparathyroidism defines diagnosis of hypoparathyroidism as marked hypocalcemia in the presence of undetectable, low or inappropriately normal intact PTH level on two occasions at least two weeks apart. The guidelines do not specify a target PTH level to indicate permanent hypoparathyroidism but suggest that levels <10 pg/mL 12-24 hours post-surgery are at risk. Additional laboratory abnormalities that can arise include elevated serum phosphate, reduction in vitamin D and increase in urine calcium excretion.
- VIII. Diagnosis and treatment of hypoparathyroidism is highly specialized. To ensure an appropriate diagnosis and that the benefits of treatment outweigh the risks, prescribing by, or in consultation with, an endocrine or nephrology specialist is required.
- IX. About 70-80% of patients with post-surgery parathyroid failure will recover within a month and therapy can be weaned. Chronic disease is defined as no adequate control of calcium and vitamin D levels despite CT for at least 6 months.
- X. The most common cause of hypoparathyroidism is related to removal or damage to the parathyroid glands during thyroid-related surgery. Symptoms and other complications can include cataracts, renal calcification, neurological manifestations and cardiac abnormalities. Conventional therapy is intended to treat hypocalcemia with therapeutic doses of elemental calcium (>600 mg/day) and active (0.25 - 3μ g/day of calcitriol) or analog ($1,000$ - $100,000$ IU per day of cholecalciferol [D3]; $50,000$ IU weekly to daily of ergocalciferol [D2]) forms of vitamin D above the daily recommended levels. Additional agents such as thiazide diuretics, magnesium supplementation, and phosphate binders can be considered in specific scenarios.
- XI. The guidelines suggest if disease control is unattainable despite treatment with conventional therapy, that parathyroid hormone (PTH) replacement can be considered. Inadequate disease control despite conventional therapy is presented as fluctuation of calcium levels, hyperphosphatemia, renal impairment or other renal-related disease or issues. Other considerations include compliance with therapy, malabsorption or GI side effects. Parathyroid

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hormone (Natpara) was approved in 2015 as an adjunct treatment along with conventional therapy for hypoparathyroid-related hypocalcemia. In 2019, the manufacturer initiated a product recall due to production issues and they indicated that it would stop all production by the end of 2024, including the special use program. The guideline does mention use of palopegteriparatide (Yorvipath) but was not FDA approved at the time of publication.

Investigational or Not Medically Necessary Uses

- I. Palopegteriparatide (Yorvipath) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
 - A. Osteoporosis
 - i. Palopegteriparatide (Yorvipath) is a prodrug analog of inert teriparatide. Teriparatide under brand name (Forteo) and generics is FDA-approved for treatment of osteoporosis. In the 52-week OLE results showed improvements to bone health related values (bone mineral density [BMD] and type 1 N-terminal propeptide [P1NP]). However, the improvements were minor and would not provide an adequate response if primarily used as an osteoporosis treatment. As of November 2024, the manufacturer confirmed that they are not actively pursuing approval in this space.
 - B. Acute post-surgical hypoparathyroidism
 - i. Palopegteriparatide (Yorvipath) was not studied in acute postsurgical hypoparathyroidism. Guidelines indicate that post-surgical PTH levels <10 pg/mL 12-24 hours could be an indication of permanent hypoparathyroidism, the risk is less than 50%. Additionally, 70-80% of individuals will likely recover within a month on conventional therapy, at which point can be gradually withdrawn.

References

1. Yorvipath. Package Insert. Ascendis Pharma; August 2024.
2. Khan AA, Bilezikian JP, Brandi ML, et al. Evaluation and Management of Hypoparathyroidism Summary Statement and Guidelines from the Second International Workshop. J Bone Miner Res. 2022;37(12):2568-2585. doi:10.1002/jbmr.4691
3. Khan AA, Rubin MR, Schwarz P, et al. Efficacy and Safety of Parathyroid Hormone Replacement With TransCon PTH in Hypoparathyroidism: 26-Week Results From the Phase 3 PaTHway Trial. J Bone Miner Res. 2023;38(1):14-25. doi:10.1002/jbmr.4726
4. Clarke BL, Khan AA, Rubin MR, et al. Efficacy and Safety of TransCon PTH in Adults with Hypoparathyroidism: 52-Week Results From the Phase 3 PaTHway Trial. J Clin Endocrinol Metab. Published online October 8, 2024. doi:10.1210/clinem/dgae693

Related Policies

Currently there are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	02/2025

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP297

Description

Palovarotene (Sohonos) is a selective retinoic-acid receptor gamma (RAR γ) agonist.

Length of Authorization

- Initial: Three months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form*	Quantity Limit
palovarotene (Sohonos)	Fibrodysplasia ossificans progressiva (FOP)	1 mg capsule	30 capsules/30 days
		1.5 mg capsule	
		2.5 mg capsule	
		5 mg capsule	
		10 mg capsule	

*See appendix for weight-based dosing for pediatric patients

Initial Evaluation

- I. **Palovarotene (Sohonos)** may be considered medically necessary when the following criteria are met:
 - A. Member is 8 years of age or older and female; **OR**
 1. Member is 10 years of age or older and male; **AND**
 - B. Documentation of weight within the last three months if under the age of 18 years; **AND**
 - C. Medication is prescribed by, or in consultation with, a specialist from the FOP centers of excellence [found here: [Research Centers - IFOPA - International Fibrodysplasia Ossificans Progressiva Association](#)]; **AND**
 - D. A diagnosis of **fibrodysplasia ossificans progressiva (FOP)** when the following are met:
 1. Documentation of the *ACVR1* mutation; **AND**
 2. Provider attestation that the member has the following clinical features:
 - i. Member has bilateral malformation of the big toes [characteristically short and laterally deviated (hallux valgus) and absent or fused joint]; **AND**
 - ii. Member has presence of soft tissue ossification
- II. Palovarotene (Sohonos) is considered investigational when used for all other conditions, including but not limited to:
 - A. Juvenile fibromatosis/desmoid tumors
 - B. Progressive osseous heteroplasia (POH)

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 palovarotene (Sohonos) continues to slow or stabilize the progression of disease and treatment provides clinical benefit to the member.

Supporting Evidence

- I. Palovarotene (Sohonos) was approved for the reduction in the volume of new heterotrophic ossification (HO) in adults and children aged eight and older for females and ten and older for males with a diagnosis of fibrodysplasia ossificans progressiva (FOP).
- II. Due to the rarity and complexity of FOP, diagnosis and treatment should be done by, or in consultation with, a physician who specializes in rare connective tissue diseases. Currently there are four centers that specialize in FOP in the continental United States, and it is recommended that the patients primary care physician consult with one in the path to treatment.
- III. FOP is an ultra-rare, genetic connective tissue disorder characterized by severe, progressive development of bone in areas outside of the skeleton (heterotopic ossification; HO), such as the ligaments, tendons, and muscles. The hallmark symptom of FOP is malformation of the big toes at birth; the big toe presents as short, bent, and usually curved inward with a missing joint. Episodes of painful soft tissue swelling, known as flare-ups, begin during the first decade of life, and these are often precipitated by soft tissue injury, intramuscular injections, viral infections, or falls. These flare-ups may lead to extra skeletal HO, which progresses throughout life. Over time, HO eventually leads to stiffness in affected areas, limited movement, and eventual ankylosis (fusion) of affected joints. Many individuals with FOP are confined to a wheelchair by their 30s, requiring lifelong assistance with activities of daily living. The estimated median lifespan of individuals with FOP is 56 years; death is often due to cardiorespiratory failure as a result of severe restriction of the chest wall.
- IV. FOP is caused by mutations in the activin A receptor type 1 gene (*ACVR1*), which encodes a bone morphogenetic protein (BMP) type I receptor that is important during the formation of the skeleton in the embryo and the repair of the skeleton following birth. The mutation in the *ACVR1* gene increases BMP signaling, resulting in the formation of heterotopic bone. Approximately 97% of patients with FOP have the same *ACVR1* point mutation (arginine to histidine [R206H]), which is considered classic FOP. A diagnosis of FOP may be confirmed by clinical evaluation, characteristic physical findings, and sequencing of the *ACVR1* gene; historically patients were confirmed by physical findings and diagnosis by elimination, the *ACVR1* gene is more routinely tested for in patients in present day. Palovarotene (Sohonos) helps decrease this BMP signaling, allowing normal tissue repair.
- V. Whole body computed tomography (WBCT) can be done to assess and track new HO; however, this is not routinely done in practice outside of the four FOP centers or in a clinical trial. The majority of providers assess patient disease progression based on physical exam and provider or patient assessment tools such as the Fibrodysplasia Ossificans Progressiva Physical Function

Questionnaire (FOP-PFQ) or the Cumulative Analogue Joint Involvement Scale (CAJIS). There are several FOP-PFQ depending on age, but those 15 and over are self-reported with 28 items rated 1 to 5 with 5 being able to do the task without help and without use of any assistive device or aid, including a wheelchair. A higher score is more normal functioning, whereas a lower score is worsened disease. CAJIS is a provider scoring of mobility limitations of 15 sites of the body (three axial: neck, jaw, thoraco-lumbar spine), six upper body and six lower body (including each shoulder, wrist, hip, socket, ankle, knee). Each site is assessed for regular movement (score zero), partially impaired (score one), and fully immobile (score two), with a higher score meaning more HO over the body and more immobilization. It is important to note that these tools are newer in development and physicians may use other non-traditional scales or monitoring to track patients, such as ability to fully expand and reach arms out from the body (assessing shoulder and elbow HO).

- VI. To date, the 2022 International Clinical Council on FOP lists management as predominantly supportive and focuses on prevention of flare-ups and improving quality of life. These preventive measures include things like preventing falls by installing handrails or wearing headgear, avoiding unnecessary surgeries, and preventing viral illnesses via hand washing and hand sanitizer, as routine immunizations may cause flares. The first line pharmaceutical treatment option is a short course of glucocorticoids taken within 24 hours of trauma and continued over three to four days to decrease HO from flare-up or the use of a nonsteroidal anti-inflammatory drug (NSAID) like ibuprofen; there is no preventive therapy in the guidelines.
- VII. Palovarotene (Sohonos) was studied in a single-arm, multicenter, 48-month, Phase 3 clinical trial (MOVE) evaluating the safety and efficacy in those with FOP using an outside control, the National Health Service's (NHS) FOP registry in untreated individuals (n=101); matched as closely as possible to those in the NHS registry by age and gender. Patients (n=99) were four years of age and older, weighing at least 10 kilograms, with a diagnosis of FOP. Patients were allowed in the study without a known *ACVR1* gene mutation, but the primary analysis only included those with the *ACVR1-R206H* gene mutation. All patients received chronic treatment, 5mg once daily, with increased dosing at the time of a flare-up or a substantial high-risk traumatic event likely to lead to a flare-up, 20 mg once daily for four weeks followed by 10 mg once daily for 8 weeks, before returning to maintenance. The primary endpoint was the annualized change in new HO volume versus untreated NHS patients measured by low-dose whole-body computed tomography [WBCT]. At the end of the 48 months, the mean annualized HO in cm³/year was 9.4 in those treated with palovarotene (Sohonos) and 20.3 in the NHS registry. This was a treatment difference of 10.9 cm³/yr (95% CI; -21.9, -0.6 p=0.039) or a reduction of 54% in the new volume with palovarotene (Sohonos) versus untreated NHS registry.
- VIII. The overall quality of evidence is considered low. Although, palovarotene (Sohonos) showed a statistically significant change in the annualized new HO volume, this is not a validated endpoint in FOP and the clinical significance of this remains unknown. Additionally, the trial did not show differences between the number of flares the patients in the trial experienced, the number of new HO sites, or quality of life measures in the patients of the study. The true significance of palovarotene (Sohonos) will be learnt in real-world application. Additionally, the International Clinical Council put out a statement in August 2023 acknowledging palovarotene (Sohonos) as the first next steps in disease treatment, but noted caution with use due to the serious adverse effects of the drug and the unknown clinical meaning of the decrease in new HO.

- IX. All patients in the trial experienced at least one adverse event (AE). The most commonly reported were mucocutaneous events such as dry skin (68.7%), lip dryness (46.5%), alopecia (34.3%), pruritus (26.3%), and musculoskeletal events such as arthralgia (33.3%). There was also a large number of dose reductions, mainly related to mucocutaneous ADE. The incidence of dose reduction was higher during flare-up treatment (34.3%) than during chronic treatment (5.1%), as was the overall incidence of dose reduction due to other TEAEs (flare-up treatment: 40.0%; chronic treatment: 11.1%). Adverse reactions leading to permanent discontinuation occurred in 11 (8%) palovarotene treated subjects with dry skin being the most common cause in 2 (1%) subjects. The label also includes a warning for embryo-fetal toxicity and premature epiphyseal closure in growing pediatric patients. The latter occurred in 21 (15%) of the 8 to 10 year or older palovarotene (Sohonos) population.

Investigational or Not Medically Necessary Uses

- I. Palovarotene (Sohonos) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
- A. Juvenile fibromatosis/desmoid tumors
 - B. Progressive osseous heteroplasia (POH)

Appendix

- I. Once daily dosing recommendation for pediatric patients aged 8 to 13 years for females and 10 to 13 for males:

Weight	Daily Dosage	Week 1 to 4 Flare-up Dosage	Week 5 to 12 Flare-up Dosage
10 kg to 19.9 kg	2.5 mg	10 mg	5 mg
20 kg to 39.9 kg	3 mg	12.5 mg	6 mg
40 kg to 59.9 kg	4 mg	15 mg	7.5 mg
≥ 60 kg	5 mg	20 mg	10 mg

References

1. Sohonos. Package Insert. Ipsen Biopharmaceuticals, Inc. Cambridge, MA. August 2023.
2. International Clinical Council on FOP (ICC) and Consultants. The Medical Management of Fibrodysplasia Ossificans Progressiva: Current Treatment Considerations. 2022. Accessed October 10, 2022. [ICC_guidelines-updated-May-2022.pdf](#)
3. Pignolo RJ, Hsiao EC, Al Mukaddam M, et al. Reduction of New Heterotopic Ossification (HO) in the Open-Label, Phase 3 MOVE Trial of Palovarotene for Fibrodysplasia Ossificans Progressiva (FOP). *J Bone Miner Res.* 2023;38(3):381-394. doi:10.1002/jbmr.4762

Policy Implementation/Update:

Action and Summary of Changes	Date
Policy created	02/2024

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP196

Description

Panobinostat (Farydak) is an orally administered histone deacetylase inhibitor.

Length of Authorization

- Initial: Six months
- Renewal: Six months (can only be renewed once)

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
panobinostat (Farydak)	10 mg capsules	Multiple Myeloma with ≥ 2 prior regimens, including bortezomib and an immunomodulatory agent	6 capsules/21 days
	15 mg capsules		
	20 mg capsules		

Initial Evaluation

- I. Panobinostat (Farydak) 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 the following are met:
 1. Provider attests member has received at least two prior regimens including both of the following:
 - i. Bortezomib (Velcade); **AND**
 - ii. Immunomodulatory agent (e.g., thalidomide, lenalidomide, pomalidomide); **AND**
 2. Provider attests panobinostat (Farydak) will be used in combination with one of the following:
 - i. Bortezomib (Velcade) AND dexamethasone *only*; **OR**
 - ii. Lenalidomide (Revlimid) AND dexamethasone *only*; **OR**
 - iii. Carfilzomib (Kyprolis) *only*
- II. Panobinostat (Farydak) 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

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; **AND**
- III. Member is responsive to treatment defined by stabilization of disease or decrease in tumor size or tumor spread; **AND**
- IV. Member will not receive more than a total treatment duration of 48 weeks; **AND**
- V. Provider attests panobinostat (Farydak) will be used in combination with one of the following:
 - A. Bortezomib (Velcade) AND dexamethasone *only*; **OR**
 - B. Lenalidomide (Revlimid) AND dexamethasone *only*; **OR**
 - C. Carfilzomib (Kyprolis) *only*

Supporting Evidence

- I. Panobinostat (Farydak) is FDA-approved for use in combination with bortezomib and dexamethasone and is indicated in the treatment of patients with multiple myeloma who have received at least two prior regimens, including bortezomib and an immunomodulatory agent. This indication is approved under accelerated approval based on progression free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.
- II. The recommended starting dose of panobinostat (Farydak) is 20 mg, taken orally once every other day for three doses per week (on Days 1, 3, 5, 8, 10, and 12) of Weeks 1 and 2 of each 21-day cycle for eight cycles. Treatment continuation may be considered for an additional eight cycles (total 16 cycles) for patients with clinical benefit, unless they have unresolved severe or medically significant toxicity. The total duration of treatment may be up to 16 cycles (48 weeks).
- III. Panobinostat (Farydak) was studied in 768 subjects from one Phase 3, double-blind, placebo-controlled, multicentered, multi-country trial. The trial included subjects with one to three previous treatments. Subjects were randomized 1:1 to receive panobinostat (Farydak) + bortezomib and dexamethasone (PAN-BTZ-Dex) or placebo + bortezomib and dexamethasone (PBO-BTZ-Dex) stratified by prior use of bortezomib and the number of prior lines of anti-myeloma therapy. The primary endpoint was progression free survival (PFS), and a key secondary endpoint was overall survival (OS).
 - Median PFS was 11.99 months (95% CI 10.33-12.94) PAN-BTZ-Dex compared to 8.08 months (95% CI 7.56-9.23) PBO-BTZ-Dex, with HR 0.63 (95% CI 0.52-0.76) $p < 0.0001$.

	Median Progression-Free Survival (95% CI, mo [n])		Hazard Ratio (95% CI)
	PAN-BTZ-Dex	Placebo-BTZ-Dex	
Prior use of immunomodulatory drugs (n=485)	13.14 (11.56-15.47)	10.41 (7.95-11.53)	0.54 (0.43-0.68)
Prior use of immunomodulatory drugs and bortezomib (n=193)	11.99 (9.69-13.90)	8.31 (6.14-12.32)	0.52 (0.36-0.76)
Previous use of immunomodulatory drugs, bortezomib, and two or more lines (n=147)	11.99 (9.69-13.37)	6.97 (4.86-13.40)	0.47 (0.31-0.72)

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- Matured median OS was 40.3 months (95% CI 35-44.8) PAN-BTZ-Dex compared to 35.8 months (95% CI 29-40.6) PBO-BTZ-Dex, with HR 0.94 (95% CI 0.78–1.14) p=0.54.

	Median Overall Survival (95% CI, mo [n])		Hazard Ratio (95% CI)
	PAN-BTZ-Dex	Placebo-BTZ-Dex	
Prior use of immunomodulatory drugs (n=485)	36.2 (31.18–41.36)	29.4 (24.57–37.78)	0.94 (0.74–1.19)
Prior use of immunomodulatory drugs and bortezomib (n=193)	27.2 (24.21–34.63)	24.7 (17.48–35.38)	1.03 (0.72–1.47)
Previous use of immunomodulatory drugs, bortezomib, and two or more lines (n=147)	25.5 (19.58–34.33)	25.5 (19.58–34.33)	1.01 (0.68–1.50)

- IV. Although the clinical trial evaluated subjects with one to three previous treatments, as stated in the package insert, the approval of panobinostat (Farydak) was based upon the efficacy and safety in a prespecified subgroup analysis of 193 patients who had received prior treatment with both bortezomib and an immunomodulatory agent and a median of two prior therapies as the benefit to risk profile appeared to be greater in this more heavily pretreated population.
- V. Panobinostat (Farydak) is associated with significant toxicity. Clinical trial discontinuation rate was 36% in the panobinostat (Farydak) group, due to adverse events, as compared to 20% in the placebo group. Moreover, discontinuation rate due to Grades 3 or 4 adverse events was 25% in the panobinostat (Farydak) group compared to 13% in the placebo group. However, split fill management is not applicable because only a total of six panobinostat (Farydak) capsules are given per 21-day cycle.
- VI. Panobinostat (Farydak) is a REMS agent, carrying a black box warning for fatal and serious toxicities of severe diarrhea and cardiac toxicities.
 - Common adverse events ($\geq 20\%$) are diarrhea, fatigue, nausea, peripheral edema, decreased appetite, pyrexia, and vomiting.
 - Common non-hematologic abnormalities ($\geq 40\%$) are hypophosphatemia, hypokalemia, hyponatremia, and increased creatinine.
 - Common hematologic abnormalities ($\geq 60\%$) are thrombocytopenia, lymphopenia, leukopenia, neutropenia, and anemia.
- VII. Per NCCN V2.2021 guidelines, panobinostat (Farydak) + bortezomib and dexamethasone is a Category 1 “other recommended regimen” for previously treated multiple myeloma. Other combinations that do not include panobinostat (Farydak) are considered “preferred”. NCCN guidelines recommend that panobinostat (Farydak) + carfilzomib (Category 2A) OR panobinostat + lenalidomide and dexamethasone (Category 2A) may be useful in certain circumstances and state that such treatment is only indicated for patients who have received at least two prior therapies, including bortezomib and an immunomodulatory agent; guidelines do not define circumstances.
 - Panobinostat (Farydak) + lenalidomide and dexamethasone was studied in a multicenter phase I/II study. Primary endpoint of phase II was ORR, which was 82%, and the clinical benefit rate was 91%.

- Panobinostat (Farydak) + carfilzomib was studied in a single-center, phase II study in 27 patients. Primary endpoint was ORR, which was 41%. PFS was 7.1 months.

Investigational or Not Medically Necessary Uses

- I. Panobinostat (Farydak) 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.

Appendix

- I. Table 1: Recommended Dosing Schedule of panobinostat (Farydak) in Combination with Bortezomib and Dexamethasone During Cycles 1 to 8

21-Day Cycle												
Cycles 1 to 8 (3-Week cycles)	Week 1 Days					Week 2 Days					Week 3	
FARYDAK	1		3		5		8		10		12	Rest period
Bortezomib	1			4			8			11		Rest period
Dexamethasone	1	2		4	5		8	9		11	12	Rest period

- II. Table 2: Recommended Dosing Schedule of panobinostat (Farydak) in Combination with Bortezomib and Dexamethasone During Cycles 9 to 16

21-Day Cycle												
Cycles 9 to 16 (3-Week cycles)	Week 1 Days					Week 2 Days					Week 3	
FARYDAK	1		3		5		8		10		12	Rest period
Bortezomib	1						8					Rest period
Dexamethasone	1	2					8	9				Rest period

- III. Table 3: 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 • melphalan • bendamustine

References

1. Farydak [Prescribing Information]. Las Vegas, NV: Secura Bio, Inc. September 2019.
2. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Multiple Myeloma Version 2.2021. 2020 September 9; National Comprehensive Cancer Network. Available from: https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf

Policy Implementation/Update:

Action and Summary of Changes	Date
Criteria transitioned to policy format. Removed requirements around counseling on side effects and attesting to lack of recent myocardial infarction or unstable angina. Addition of supporting evidence and additional combination agent options [addition of lenalidomide (Revlimid) and dexamethasone; or carfilzomib (Kyprolis)].	10/2020
Criteria created	03/2015

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP167

Description

Parathyroid hormone (Natpara) is subcutaneously administered, FDA-approved hormone replacement therapy for hypoparathyroidism. Parathyroid hormone acts to regulate the body's calcium levels.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
Parathyroid hormone (Natpara)	25 mcg/dose cartridge	Adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism	2 cartridges/28 days
	50 mcg/dose cartridge		2 cartridges/28 days
	75 mcg/dose cartridge		2 cartridges/28 days
	100 mcg/dose cartridge		2 cartridges/28 days

Initial Evaluation

- I. Parathyroid hormone (Natpara) may be considered medically necessary when the following criteria below are met:
 - A. Member is being treated for hypocalcemia due to hypoparathyroidism; **AND**
 - B. Member does not have following:
 1. Hypoparathyroidism due to calcium-sensing receptor mutations
 2. Acute post-surgical hypoparathyroidism; **AND**
 - C. Member does not have a history of Page's disease of bone, open epiphyses, radiation therapy involving the skeleton, or hereditary disorders predisposing to osteosarcoma; **AND**
 - D. Member has tried and failed treatment with calcium supplements and active forms of vitamin D (e.g. calcitriol); **AND**
 - E. Member will be treated with this medication adjunct to calcium and vitamin D
- II. Parathyroid hormone (Natpara) is considered investigational when used for all other conditions, including but not limited to:
 - A. Hypoparathyroidism due to calcium-sensing receptor mutation
 - B. Acute post-surgical hypoparathyroidism

Renewal Evaluation

- I. Member has received a previous prior authorization approval for this agent through the 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 improvement or stability of disease symptoms

Supporting Evidence

- I. Parathyroid hormone (Natpara) is FDA approved as adjunctive therapy with calcium + vitamin D to control hypocalcemia in patients with hypoparathyroidism.
- II. Parathyroid hormone (Natpara) acts to regulate the body's calcium levels. Parathyroid hormone increases the rate of bone turnover by stimulating osteoclast and osteoblast activity, which leads to calcium resorption from bone. The net effects of parathyroid hormone are increases in serum calcium and magnesium concentration and decreased phosphate concentration.
- III. Parathyroid hormone (Natpara) has not been studied in patients with hypoparathyroidism due to calcium sensing receptor mutation or patients with acute post-surgical hypoparathyroidism.
- IV. Parathyroid hormone (Natpara) has a Black Box warning for use in patients with increased risk of osteosarcoma. Due to this potential risk, parathyroid hormone (Natpara) should be used only in patients who cannot be well-controlled on calcium and active forms of vitamin D.

Investigational Uses

- I. Parathyroid hormone (Natpara) is not intended for use in members with hypoparathyroidism due to calcium-sensing receptor mutations, or acute post-surgical hypoparathyroidism.

References

1. Natpara [Prescribing Information]. Lexington, MA: Shire-NPS Pharmaceuticals, Inc., 2018.

Policy Implementation/Update:

Date Created	January 2015
Date Effective	January 2015
Last Updated	November 2019
Last Reviewed	11/2019

Action and Summary of Changes	Date
Criteria updated to new policy format.	11/2019

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP146

Description

Teriparatide, teriparatide (Forteo), and abaloparatide (Tymlos) are human parathyroid hormone related peptide [PTHrP (1-34)] analogs.

Length of Authorization

- Initial: 12 months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
teriparatide (Forteo) generic teriparatide	Primary Osteoporosis/Hypogonadal-related Osteoporosis in Men	600 mcg/2.4 mL pen-injector	1 pen (2.4 mL)/28 days
teriparatide (biosimilar formulation)	Post-Menopausal Osteoporosis in Women Glucocorticoid-induced Osteoporosis	620 mcg/2.48 mL pen-injector	1 pen (2.48 mL)/28 days
abaloparatide (Tymlos)	Primary Osteoporosis/Hypogonadal-related Osteoporosis in Men Post-Menopausal Osteoporosis in Women	3120 mcg/1.56 mL (2000 mcg/mL)	1 pen (1.56 mL)/30 days

Initial Evaluation

- I. **Abaloparatide (Tymlos), teriparatide (biosimilar formulation), generic teriparatide, and teriparatide (Forteo)** may be considered medically necessary when the following criteria below are met:
 - A. Member is 18 years of age or older; **AND**
 - B. Member will not have received treatment with a parathyroid hormone for more than two years during their lifetime; **OR**
 1. Member will have received treatment with a parathyroid hormone for more than two years during their lifetime; **AND**
 - i. Provider attestation that patient remains, or has returned to, having high or very high fracture risk (e.g., a fracture in the past 12 months, a fracture while on osteoporosis therapy, a history of multiple fractures, fractures while on long-term glucocorticoids, T-score ≤ -3.0 , high risk for falls or a history of injurious falls, a FRAX 10-year probability for major fracture $>30\%$ or hip fracture $>4.5\%$, etc.); **AND**

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These criteria do not imply or guarantee approval. Please check with your plan to ensure coverage. Preauthorization requirements are only valid for the month published. They may have changed from previous months and may change in future months.

- C. Medication will not be used in combination with other osteoporotic agents [e.g., denosumab (Prolia), bisphosphonates (alendronate, risedronate, ibandronate, zoledronic acid injection), calcitonin nasal spray, or raloxifene]; **AND**
- D. One of the following fracture risk categories is met:
 - 1. Member has a fracture of the hip or spine regardless of BMD; **OR**
 - 2. Member has a T-score ≤ -2.5 in spine, femoral neck, total hip or 1/3 radius; **OR**
 - 3. Member has a T-score ≤ -1 and a history of recent fracture of proximal humerus, pelvis, or distal forearm; **OR**
 - 4. Member has a T-score between -1 and -2.5 with a FRAX 10-year probability for major fracture $\geq 20\%$ or hip fracture $\geq 3\%$; **AND**
- E. Provider attestation or clinical of treatment failure or ineffective response to one of the following, unless all are contraindicated (*Please note: These agents may be subject to prior authorization or step therapy and may require an additional review):
 - 1. Oral bisphosphonate (e.g., alendronate, ibandronate), **OR**
 - 2. Intravenous bisphosphonate (e.g., zoledronic acid injection*); **OR**
 - 3. Denosumab (Prolia)*; **AND**
- F. For abaloparatide (Tymlos), a diagnosis of one of the following:
 - 1. **Post-Menopausal Osteoporosis in Women; OR**
 - 2. **Primary Osteoporosis/Hypogonadal-related Osteoporosis in Men; OR**
- G. For teriparatide (biosimilar formulation), a diagnosis of one of the following:
 - 1. **Post-Menopausal Osteoporosis in Women; OR**
 - 2. **Primary Osteoporosis/Hypogonadal-related Osteoporosis in Men; OR**
 - 3. **Glucocorticoid-induced Osteoporosis; OR**
- H. For generic teriparatide, a diagnosis of one of the following:
 - 1. **Post-Menopausal Osteoporosis in Women; AND**
 - i. Treatment with abaloparatide (Tymlos) AND teriparatide (biosimilar formulation) have been ineffective, not tolerated, or contraindicated; **OR**
 - 2. **Primary Osteoporosis/Hypogonadal-related Osteoporosis in Men; AND**
 - i. Treatment with abaloparatide (Tymlos) AND teriparatide (biosimilar formulation) have been ineffective, not tolerated, or contraindicated; **OR**
 - 3. **Glucocorticoid-induced Osteoporosis; AND**
 - i. Member is taking ≥ 5 mg prednisone or its equivalent daily with an anticipated duration of ≥ 3 months; **AND**
 - ii. Treatment with teriparatide (biosimilar formulation) has been ineffective, not tolerated or contraindicated; **OR**
- I. For BRAND teriparatide (Forteo), a diagnosis of one of the following:
 - 1. **Post-Menopausal Osteoporosis in Women; AND**
 - i. Treatment with abaloparatide (Tymlos), teriparatide (biosimilar formulation) AND generic teriparatide have been ineffective, not tolerated, or contraindicated; **OR**
 - 2. **Primary Osteoporosis/Hypogonadal-related Osteoporosis in Men; AND**
 - i. Treatment with abaloparatide (Tymlos), teriparatide (biosimilar formulation) AND generic teriparatide have been ineffective, not tolerated, or contraindicated; **OR**

3. **Glucocorticoid-induced Osteoporosis; AND**
 - i. Member is taking ≥ 5 mg prednisone or its equivalent daily with an anticipated duration of ≥ 3 months; **AND**
 - ii. Treatment with teriparatide (biosimilar formulation) AND generic teriparatide has been ineffective, not tolerated or contraindicated
- II. Parathyroid hormones are considered investigational when used for all other conditions, including but not limited to:
 - A. Osteoporosis prophylaxis
 - B. Promote fracture healing
 - C. Promote post-fusion healing
 - D. The use of abaloparatide (Tymlos) for glucocorticoid-induced osteoporosis.

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 other osteoporotic agents [e.g., denosumab (Prolia), bisphosphonates (alendronate, risedronate, ibandronate, zoledronic acid injection), calcitonin nasal spray, or raloxifene]; **AND**
- IV. If the request is for BRAND teriparatide (Forteo), treatment with teriparatide (biosimilar formulation) and generic teriparatide has been ineffective, not tolerated or contraindicated; **AND**
- V. If the request is for generic teriparatide, treatment with teriparatide (biosimilar formulation) has been ineffective, not tolerated or contraindicated; **AND**
- VI. Member has not received treatment with parathyroid hormone for more than a total of two years during their lifetime; **AND**
 - A. Provider attestation that member has demonstrated clinical improvement or stability of osteoporosis (e.g., stable, or improved bone mineral density (BMD), reduction in or no new fracture(s), reduction in fracture risk) with parathyroid hormone therapy; **OR**
- VII. Member will have received treatment with a parathyroid hormone for more than two years during their lifetime; **AND**
 - A. Provider attestation that patient remains or has returned to having high or very high fracture risk (e.g., a fracture while on osteoporosis therapy, a history of multiple fractures, fractures while on long-term glucocorticoids, T-score ≤ -3.0 , high risk for falls or a history of injurious falls, a FRAX 10-year probability for major fracture $>30\%$ or hip fracture $>4.5\%$, etc.)

Supporting Evidence

- I. Osteoporosis is characterized by decreased bone mass and increased fracture risk, most commonly at the spine, hip, and wrist. The definition of osteoporosis with high risk of fracture is defined for men and women as BMD T-score of spine, femoral neck, and/or total hip <-2.5

without fracture, having history of hip or vertebral fracture regardless of BMD, T-score ≤ -1 and a history of recent fracture of proximal humerus, pelvis, or distal forearm, T-score between -1.0 and -2.5 in the spine, femoral neck, or total hip with a -20% 10-year FRAX risk of any fracture or -3% risk of hip fracture, and receiving long-term glucocorticoid doses greater than or equal to prednisone 7.5mg per day. Although BMD is a surrogate marker, meta-analyses have found that treatment-related changes in BMD after 24 months were significantly associated with hip, vertebral, and nonvertebral fracture risk reduction in men and women with osteoporosis. Bone turnover markers (BTM) also reflect the pharmacological response to osteoporosis therapies and decline in BTM largely contributes to antifracture effect. It is suggested that BTM is used in clinical studies to compliment BMD in assessing pharmacological response to treatment.

- II. The maximum duration of use for parathyroid hormone agents (e.g., abaloparatide, teriparatide) is two years. As of November 2021, the safety and efficacy of these therapies remains undetermined. Treatment guidelines [e.g., Endocrine Society, American Association of Clinical Endocrinologists (AACE), American College of Endocrinology (ACE), American College of Rheumatology (ACR)] continue to recommend that use of parathyroid analogs be limited to 2 years. If further therapy is warranted, transition to bisphosphonates, denosumab, or raloxifene should be considered to maintain bone density gains experienced from PTH agents.
 - A. In November 2020, teriparatide (Forteo) prescribing information was revised to indicate that use beyond two years may be considered if the patient remains, or has returned to, having high fracture risk. The black box warning for high risk of osteosarcoma was removed based on the results of three retrospective claims studies that did not indicate an increased risk of osteosarcoma associated with the use of teriparatide (Forteo). At this time, it is recognized that there is conflicting evidence for increased osteosarcoma risk with PTH therapies; however, there remains lack of evidence for safety and efficacy beyond two years of therapy. Further research is needed to determine the risk/benefit profile and medical necessity of extended therapy.
 - B. It is reasonable to consider extending duration of therapy beyond two years in patients who remain, or have returned to, having high or very high fracture risk when benefits of extended therapy outweigh the risks. Examples of this patient population may include, but are not limited to, a fracture while on osteoporosis therapy, a history of multiple fractures, fractures while on long-term glucocorticoids, T-score ≤ -3.0 , high risk for falls or a history of injurious falls, a FRAX 10-year probability for major fracture $>30\%$ or hip fracture $>4.5\%$, etc.
- III. There is lack of head-to-head trials evaluating comparative efficacy and safety of PTH analogs, teriparatide (Forteo), teriparatide biosimilar, and abaloparatide (Tymlos). Therefore, clinical superiority of one agent over the other is not established at this time. All PTH analogs have been evaluated against placebo and were found to increase BMD and/or reduce fracture risk, depending on the indication. Given the known safety, efficacy, and cost-effectiveness, trial of abaloparatide (Tymlos) is required prior to use of teriparatide biosimilar and teriparatide (Forteo) in the indicated populations.
- IV. **Post-Menopausal Osteoporosis in Women:**
 - A. The safety and efficacy of once-daily teriparatide (Forteo) and teriparatide, with a median exposure to treatment of 19 months, was examined in a double-blind, multicenter, placebo-controlled clinical study of 1637 postmenopausal women with

osteoporosis (FORTEO 20 mcg, n=541). The absolute risk reduction for new fracture in favor of teriparatide (Forteo) was a 9.3% reduction in vertebral fracture: 95% CI (5.5 – 13.1).

- B. The safety and efficacy of abaloparatide (Tymlos) was evaluated in an 18-month, randomized, multicenter, double-blind, placebo-controlled clinical trial in postmenopausal women aged 49 to 86 years (mean age of 69) who were randomized to receive abaloparatide (Tymlos) 80 mcg (N = 824) or placebo (N = 821). The absolute risk reduction for fractures in favor of abaloparatide (Tymlos) was 3.6% reduction in vertebral fractures: 95% CI (2.1 – 5.4).
- C. The 2020 AACE/ACE guidelines treatment recommendations are as follows:
 - i. Initial treatment for high fracture risk: alendronate, denosumab, risedronate, or zoledronate (strong recommendation, high quality evidence)
 - ii. Treatment for very-high fracture risk or patients, who cannot tolerate or adhere to oral bisphosphonates: zoledronate, abaloparatide, denosumab, romosozumab, teriparatide, and (strong recommendation, high quality evidence).
 - iii. Follow-up treatment after parathyroid hormone: bisphosphonate or denosumab
- D. Additionally, the 2020 Endocrine Society guidelines recommend bisphosphonates as initial treatment for high-risk patients, while denosumab may be considered as an alternative initial treatment (strong recommendation, high quality evidence). For patients with a very high risk of fracture, teriparatide and abaloparatide are recommended (strong recommendation, moderate quality evidence). It is recommended that antiresorptive therapies follow treatment with parathyroid hormones.
- E. The majority of efficacy and safety data for the recommended pharmacologic treatments of postmenopausal osteoporosis are rooted in trials of bisphosphonates, which have reported robust long-term efficacy and relative safety. Similarly, denosumab (Prolia) has well established long-term safety and efficacy as an initial treatment option. Alternatively, recommendations for use of parathyroid hormone therapy in the first-line setting for patients with severe osteoporosis or very high fracture risk are primarily supported only by Phase 3 studies that compared teriparatide to bisphosphonates: NCT00051558, NCT00343252 and the VERO study. While these studies showed statistically significant improvements with teriparatide in surrogate markers related to osteoporosis (e.g., BMD changes, reduction in pain severity, and incidence of vertebral fracture) when compared to a bisphosphonate, they are confounded due to factors such as small sample sizes, high dropout rates, and high previous exposure to bisphosphonates. Additionally, clinical meaningfulness remains uncertain due to lack of longer-term applicability to broader osteoporosis population, and lack of outcomes related to long-term morbidity; thus, the overall quality of evidence is considered low to moderate and may not be sufficient to drive clinical decisions. As such, weighing the safety, efficacy, cost, and clinical experience, oral and intravenous bisphosphonates and denosumab (Prolia) are considered standard and appropriate high-value treatment options in this setting.

V. Primary Osteoporosis/Hypogonadal-related Osteoporosis in Men

- A. The safety and efficacy of once-daily teriparatide (Forteo) and teriparatide injection was examined in a double-blind, multicenter, placebo-controlled clinical study of 437 men with either primary (idiopathic) or hypogonadal osteoporosis (n=151) for a median exposure of 10 months. Patients were included if they were 30-85 years old, ambulatory, free of chronic conditions and lumbar or proximal spine BMD of at least 2 standard deviations below the average. Baseline characteristics were similar in all groups: mostly 99% white, average age 59 years, BM 25kg/m², and average lumbar BMD T-score -2.2. The primary endpoint, change in lumbar spine bone mass density (BMD) from baseline, was met in 94% of men treated. Fifty-three percent of patients treated with teriparatide (Forteo) achieved at least a 5% increase in spine BMD, and fourteen percent of patients gained ≥10% in spine BMD.
- B. The safety and efficacy of once-daily abaloparatide (Tymlos) was examined in a 12-month double-blind, multicenter, placebo-controlled clinical study with 228 men with primary or hypogonadal osteoporosis with high risk of fracture. The primary endpoint was percent change in lumbar spine BMD from baseline at 12 months. Men 40-85 years old were included if they had a diagnosis of osteoporosis (T-scores ≤ -2.5 and > -3.5 at the lumbar spine, total hip, or femoral neck, >65 years of age with BMD T-scores ≤ -2.0 (based upon the male reference database) and stable hydroxyvitamin D levels. Baseline characteristics were similar across both groups: mean age 68.3 years, mean lumbar spine BMD T-score -2.1, mean BMI 26.5 kg/m², 56.6% of patients had prior fractures. The mean change in BMD at lumbar spine at 12 months for the abaloparatide (Tymlos) group was 8.48% compared to placebo, 1.17% (p<0.001). No new safety concerns with abaloparatide (Tymlos) were observed and several of the most frequently reported AEs in men were also among the most frequent previously reported in the ACTIVE study in women (dizziness, arthralgia, upper respiratory tract infection, headache, hypertension, and nasopharyngitis).
- C. According to the 2020 AACE/ACE guidelines, first-line treatment for men with osteoporosis are bisphosphonates and denosumab may be considered as an alternative initial treatment (strong recommendation, high quality evidence). Selection of therapy is based on individualized factors such as gastrointestinal problems and concomitant androgen deprivation therapy. The National Osteoporosis Foundation (NOF), Endocrine Society, and AACE/ACE guidelines recommend that alendronate, risedronate, zoledronate and denosumab have evidence for “broad-spectrum” antifracture efficacy and should be, in the absence of contraindications, be considered as first line therapy in treatment of osteoporosis. According to the 2012 Endocrine Society guidelines, it is recommended that initial treatment of osteoporosis in men with recent hip fracture should receive zoledronic acid (strong recommendation, low quality evidence), while men with high fracture risk on testosterone should receive an effective anti-fracture agent such as a bisphosphonate or teriparatide (conditional recommendation, low quality evidence). Teriparatide (Forteo) is recommended in treatment of men and women with osteoporosis with upper or lower gastrointestinal problems, when nonoral therapy is preferred, or when patients cannot tolerate or do not respond adequately to bisphosphonates. Guidelines have not been updated to include abaloparatide (Tymlos) in therapy recommendations in men with osteoporosis.

- D. The guidelines note that there is increasing evidence to support that BMD gains may be greater when an anabolic drug is administered before the antiresorptive drug compared with the opposite sequence in patients with high-risk fracture. The 2022 NOF guidelines states that when sequential treatment is considered in patients with recent fractures and/or very low BMD (e.g., T-score < - 3.0), starting with anabolic therapy following an antiresorptive agent is preferred. The 2020 AACE/ACE guidelines also note that it probably is not advisable to use teriparatide (or abaloparatide) if denosumab is stopped. It is hypothesized that bone resorption is required, in part, for PTH analogs to stimulate new bone formation. If antiresorptive agents are suppressing bone resorption, the anabolic action of PTH analogs may be impaired. Although the 2022 NOF and 2020 AACE/ACE guidelines note that sequential therapy (anabolic preceding antiresorptive) may be considered in patients with recent fractures and/or very low BMD, the quality of evidence supporting this statement is low. There are three low quality studies which explored the question of sequential therapy. The studies should not be used for medical decision making due to small study populations, lack of blinding, lack of adherence assessment, and inconsistent BMD outcomes. More research is necessary to determine efficacy and appropriateness of sequential therapy at this time.
- i. The DATA-switch study (Leder et al) was a randomized cross over study investigating the effect of sequential osteoporosis therapy in BMD in 77 postmenopausal women, 45 years or older, with osteoporosis. Participants were randomized 1:1:1 to receive teriparatide 20 mcg daily for 24 months then switched to denosumab 60mg every 6 months, denosumab every 6 months for 24 months then switched to teriparatide daily, or denosumab and teriparatide for 24 months, then switched to denosumab every 6 months. BMD at the spine, hip, and wrist were measured at 6, 12, 18, and 24 months after switching therapy. The primary endpoint, percent change in spine BMD over 4 years, was not statistically significant between all three groups (18.3%, 14.0% and 16.0%, p=0.13). The secondary outcome, hip BMD increase, was greater in the teriparatide to denosumab group (6.6%, 95% CI 5.3-7.9) compared to denosumab to teriparatide (2.8%, 95% CI 1.3-4.2), p=0.0002. After 48 months, radius bone mineral density was unchanged in the teriparatide to denosumab group (0.0% [95% CI -1.3 to 1.4]), whereas it decreased by -1.8% (-5.0 to 0.3), p=0.0075, in the denosumab to teriparatide group, and increased by 2.8% (1.2-4.4), p=0.0099, in the combination to denosumab group.
 - a. The study is of low quality with concerns regarding validity of results due to open label study design, and a small size of the population studied. The primary endpoint did not meet statistical significance and the results of the secondary endpoints were inconsistent. Therefore, specific clinical impact of the transient bone loss that occurs in women switching from denosumab to teriparatide cannot be precisely estimated.
 - II. The DATA-Switch HR-pQCT study (Tsai et al) assessed the effects of sequential therapy on bone microarchitecture and strength at the distal tibia and radius in the DATA-Switch population. Study results found that women switching from teriparatide to denosumab had an increase in tibial BMD (net 48-month change -

0.8% $\pm$ 2.4%) and combination-to-denosumab groups (net 48-month changes +2.4% $\pm$ 4.1%) and decreased in the denosumab to teriparatide group (net 48-month change -3.4% $\pm$ 3.2%, $p < 0.001$). Changes in total volumetric BMD followed similar patterns. Tibial cortical porosity increased in the denosumab-to-teriparatide group (+16.2% $\pm$ 11.5%, $p < 0.05$ versus other groups).

- a. The study is of low quality with concerns regarding validity of results due to open label study design and a small size of the population studied. Guidelines recommend that when spine and hip BMD are not evaluable, distal radius may be evaluated for initiation of therapy or therapy monitoring. Spine fractures are more common than hip and radius fractures. Hip fractures typically result in more severe outcomes such as increase in one-year mortality rate and loss of independence. Tibial BMD change and porosity trends may demonstrate changes in microarchitecture that influence bone strength at the tibia. However, tibia BMD values are not typically measured at baseline and there is uncertain applicability and value of these study results.

- III. A European open-label, prospective, randomized trial (Obermayer-Pietsch, et al) evaluated the efficacy of osteoporosis sequential treatment regimens in 503 postmenopausal women with osteoporosis who received 24 months of teriparatide. The participants were divided into three groups based on prior antiresorptive treatment (treatment naïve, N=84, pretreated with no evidence of inadequate response to antiresorptive treatment, N=134, and pretreated with inadequate response, N=285). The majority of patients previously treated with antiresorptive treatment were treated with bisphosphonates, most commonly alendronate (86.6% and 93.0%). The primary endpoint was change in BMD at lumbar spine and secondary endpoints were changes in total hip BMD and femoral neck BMD. The mean gain in lumbar BMD was greater in the treatment naïve group (13.1%) compared to the pretreated without response (10.2%, $p < 0.005$) and pretreated with inadequate response (9.8%, $p < 0.001$). The mean gain in total hip BMD were 3.8%, 2.3%, and 2.3%, respectively. The difference in femoral neck BMD between the treatment-naïve and the inadequate responder subgroups was significant after 12 months, however, the mean changes were not significantly different across the three groups at 24 months (4.8%, 3.4%, 3.9%). The study concluded that the prior antiresorptive treatment blunted the BMD response to teriparatide.

- a. There is low confidence in the study as it was open label, adherence was not addressed, and clinically meaningful differences in change of BMD is currently unknown, therefore it is difficult to draw conclusions. Additionally, confidence in study results is uncertain as the results in change in BMD across lumbar spine, total hip and femoral neck are inconsistent. The study showed increase in BMD at lumbar spine and hip, but no statistical difference at the femoral neck. Limitations in the study precludes drawing conclusions regarding sequential therapy.

VI. **Glucocorticoid-induced osteoporosis:**

- A. The efficacy of teriparatide (Forteo) and teriparatide injection was assessed in a randomized, double blind, active-controlled trial of 428 patients (19% men, 81% women) aged 22 to 89 years (mean 57 years) treated with ≥ 5 mg/day prednisone or equivalent for a minimum of 3 months. The duration of the trial was 18 months with 214 patients exposed to teriparatide (Forteo). In patients treated with teriparatide (Forteo), the mean percent change in BMD from baseline to endpoint was 7.2% at the lumbar spine, 3.6% at the total hip, and 3.7% at the femoral neck ($p < 0.001$ all sites).
- B. According to the 2017 ACR guidelines, in adults with glucocorticoid-induced osteoporosis regardless of fracture risk, initial treatment should include oral bisphosphonates. In patients who had a fracture in the past 18 months or lost $>10\%$ bone density per year, IV bisphosphonates, teriparatide, or denosumab be used in the second-line setting; in patients who remain at moderate-to-high fracture risk, treatment should continue with a bisphosphonate, or may be switched to an alternative class (conditional recommendation, low quality of evidence).

Investigational or Not Medically Necessary Uses

- I. Osteoporosis Prophylaxis
 - A. There is currently no evidence to support the use of parathyroid hormones for the prevention of postmenopausal osteoporosis.
- II. Promote fracture healing and/or post fusion healing
 - A. There is limited safety and efficacy evidence to support the use of parathyroid hormones in the setting of fracture healing and/or post fusion healing.
- III. Abaloparatide (Tymlos) is only FDA-approved for the treatment of postmenopausal osteoporosis and primary/hypogonadal-related osteoporosis in men; there is currently a lack of sufficient evidence regarding safety and efficacy in other settings.

References

1. Forteo [Prescribing Information]. Indianapolis, IN: Eli Lilly and Company. September 2021.
2. Tymlos [Prescribing Information]. Waltham, MA: Radius Health, Inc. April 2021.
3. Teriparatide [Prescribing Information]. Morristown, NJ: Alvogen, Inc. November 2019.
4. Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists/American College of Endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis-2020 update. *Endocr Pract.* 2020;26(Suppl 1):1-46.
5. Shoback D, Rosen CJ, Black DM, Cheung AM, Murad MH, Eastell R. Pharmacological management of osteoporosis in postmenopausal women: an Endocrine Society guideline update. *J Clin Endocrinol Metab.* 2020;105(3):dgaa048.
6. Watts NB, Adler RA, Bilezikian JP, et al. Osteoporosis in men: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2012;97(6):1802-1822.
7. Buckley L, Guyatt G, Fink HA, et al. 2017 American College of Rheumatology guideline for the prevention and treatment of glucocorticoid-induced osteoporosis. *Arthritis Rheumatol.* 2017;69(8):1521-1537.
8. Saag KG, Shane E, Boonen S, et al. Teriparatide or alendronate in glucocorticoid-induced osteoporosis. *N Engl J Med.* 2007;357(20):2028-2039.
9. Hadji P, Zanchetta JR, Russo L, et al. The effect of teriparatide compared with risedronate on reduction of back pain in postmenopausal women with osteoporotic vertebral fractures. *Osteoporos Int.* 2012;23(8):2141-2150.
10. Kendler DL, Marin F, Zerbini CAF, et al. Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (Vero): a multicentre, double-blind, double-dummy, randomised controlled trial. *Lancet.* 2018;391(10117):230-240.

11. Miller PD, Lewiecki EM, Krohn K, Schwartz E. Teriparatide: Label changes and identifying patients for long-term use. *CCJM*. 2021;88(9):489-493.
12. Czerwinski E, Cardona J, Plebanski R, et al. The Efficacy and Safety of Abaloparatide-SC in Men With Osteoporosis: A Randomized Clinical Trial [published online ahead of print, 2022 Oct 3]. *J Bone Miner Res*. 2022;10.1002/jbmr.4719.
13. Watts NB, Adler RA, Bilezikian JP, et al. Osteoporosis in men: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2012;97(6):1802-1822.
14. LeBoff MS, Greenspan SL, Insogna KL, et al. The clinician's guide to prevention and treatment of osteoporosis [published correction appears in *Osteoporos Int*. 2022 Jul 28;:]. *Osteoporos Int*. 2022;33(10):2049-2102.
15. Leder BZ, Tsai JN, Uihlein AV, et al. Denosumab and teriparatide transitions in postmenopausal osteoporosis (the DATA-Switch study): extension of a randomised controlled trial. *Lancet*. 2015;386(9999):1147-1155.
16. Tsai JN, Nishiyama KK, Lin D, et al. Effects of Denosumab and Teriparatide Transitions on Bone Microarchitecture and Estimated Strength: the DATA-Switch HR-pQCT study [published correction appears in *J Bone Miner Res*. 2019 May;34(5):976]. *J Bone Miner Res*. 2017;32(10):2001-2009.
17. Finkelstein JS, Wyland JJ, Lee H, Neer RM. Effects of teriparatide, alendronate, or both in women with postmenopausal osteoporosis. *J Clin Endocrinol Metab*. 2010;95(4):1838-1845.
18. Obermayer-Pietsch BM, Marin F, McCloskey EV, et al. Effects of two years of daily teriparatide treatment on BMD in postmenopausal women with severe osteoporosis with and without prior antiresorptive treatment. *J Bone Miner Res*. 2008;23(10):1591-1600.

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
denosumab (Prolia)	Post-menopausal Osteoporosis in Women
	Osteoporosis in Men
	Increase Bone Mass in Women with Breast Cancer receiving Aromatase Inhibitor Therapy
	Increase Bone Mass in Men with Non-metastatic Prostate Cancer receiving Androgen Deprivation Therapy
	Glucocorticoid-induced Osteoporosis

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated criteria of treatment failure with bisphosphonates or Prolia to allow attestation and removed minimum 12-month trial requirement.	03/2024
Added generic teriparatide to policy with step through teriparatide (biosimilar formulation) and abaloparatide (Tymlos).	02/2024
Updated dosage forms to be reflective of product availability rather than concentration.	11/2023
Updated initial criteria requiring trial of abaloparatide (Tymlos) and teriparatide (biosimilar formulation) prior to brand Forteo. Updated renewal of brand Forteo to require teriparatide (biosimilar formulation) or abaloparatide (Tymlos).	02/2023
Updated criteria to include abaloparatide (Tymlos) in treatment of primary/hypogonadal-related osteoporosis in men. Included criteria regarding fractures despite BMD changes under fracture risk category. Removed primary/hypogonadal-related osteoporosis from investigational section. Added supporting evidence for new indication in osteoporosis in men and sequential therapy. Added related policies section.	12/2022
Added initial and renewal criteria for use beyond two years to demonstrate fracture risk remains high, refined diagnosis criteria to target patients with high fracture risk, and adjusted previous medication trials to require PO, IV bisphosphonate or Prolia while removing raloxifene and calcitonin. Updated and reformatted supporting evidence for limitation on duration of use and requirement of bisphosphonates or Prolia.	12/2021
Added criteria for the biosimilar teriparatide, requiring trial of the biosimilar prior to brand Forteo	11/2020
Added detail around maximum duration of approval [26 (monthly) fills] in order to provide more clarity around fill history. Addition of supporting evidence regarding maximum two year treatment duration	04/2020

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Added in fill count to renewal duration, as well as updated to reflect a 28-day supply instead of 30-days in the Forteo QL table	02/2020
Criteria transitioned into policy format with the following additions: supporting evidence, investigational section, and a list of drugs that should not be used in combination with parathyroid hormones. Guidelines reviewed, and the following updates were made: differentiate between T-scores without fragility fracture and with fragility fracture, defined high risk fractures, and provided inclusion criteria for glucocorticoid-induced osteoporosis.	12/2019
Update criteria to include abaloparatide (Tymlos)	08/2017
Reviewed	10/2005, 01/2007, 12/2008, 06/2013, 02/2016, 06/2017, 12/2019
Date effective	03/2016
Policy created	09/2005

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP183

Description

Peanut allergen powder-dnfp (Palforzia) is an oral immunotherapy FDA-approved for the mitigation of allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanuts. The mechanism of action is unknown at this time.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
peanut allergen powder-dnfp (Palforzia)	Peanut allergy	0.5 mg – 6 mg capsule sprinkle	13 capsule sprinkles/1 day
		3 mg daily dose capsule sprinkle	45 capsule sprinkles/15 days
		6 mg daily dose capsule sprinkle	90 capsule sprinkles/15 days
		12 mg daily dose capsule sprinkle	45 capsule sprinkles/15 days
		20 mg daily dose capsule sprinkle	15 capsule sprinkles/15 days
		40 mg daily dose capsule sprinkle	30 capsule sprinkles/15 days
		80 mg daily dose capsule sprinkle	60 capsule sprinkles/15 days
		120 mg daily dose capsule sprinkle	30 capsule sprinkles/15 days
		160 mg daily dose capsule sprinkle	60 capsule sprinkles/15 days
		200 mg daily dose capsule sprinkle	30 capsule sprinkles/15 days
		240 mg daily dose capsule sprinkle	60 capsule sprinkles/15 days
		300 mg titration powder pack	15 capsule sprinkles/15 days
		300 mg maintenance capsule sprinkle powder pack	30 capsule sprinkles/30 days

Initial Evaluation

- I. **Peanut allergen powder-dnfp (Palforzia)** may be considered medically necessary when the following criteria are met:
 - A. Member is one to 17 years of age and request is for initial dose escalation; **OR**
 1. Member is one years of age or older and is up-dosing; **AND**
 - B. Medication is prescribed by, or in consultation with, an allergist or immunologist; **AND**
 - C. The medication will not used in combination with Viaskin™ Peanut patch or other peanut desensitization therapy; **AND**
 - D. A diagnosis of **peanut allergy** when the following are met:
 1. Documented medical history of severe peanut allergy, with reactions that cannot be managed with conventional therapies such as antihistamines (e.g., reaction causes anaphylaxis, requires epinephrine use, allergy that can be triggered by smell); **AND**

2. Must have a current prescription for epinephrine; **AND**
 3. Medication used in conjunction with peanut-avoidant diet; **AND**
 4. Member does not have severe or uncontrolled asthma; **AND**
 5. Member does not have eosinophilic esophagitis or other eosinophilic gastrointestinal disease.
- II. **Peanut allergen powder-dnfp (Palforzia)** is considered investigational when used for all other conditions, including but not limited to:
- A. Initial dose escalation in members 18 years of age and older

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 is one to 17 years of age; **OR**
 - A. Member is one year of age or older and is up-dosing or using as maintenance; **AND**
- IV. Member must have a current prescription for epinephrine; **AND**
- V. Medication must be used in conjunction with peanut-avoidant diet; **AND**
- VI. Member does not have severe or uncontrolled asthma; **AND**
- VII. Member does not have eosinophilic esophagitis or other eosinophilic gastrointestinal disease; **AND**
- VIII. The medication will not be used in combination with Viaskin™ Peanut patch or other peanut desensitization therapy

Supporting Evidence

- I. The pivotal Phase 3 double-blind, placebo-controlled trial (PALISADE) leading to FDA-approval of peanut allergen powder-dnfp (Palforzia) consisted of 551 subjects aged 4 through 55 years with peanut allergy. However, the primary efficacy analysis population included only those aged 4-17 years as there were very few patients 18 years and older in the trial. Thus, FDA-approval is specific to patients aged 4 through 17 years, although Up-Dosing and Maintenance may be continued in patients 4 years of age and older. To date, there is insufficient evidence to support the initiation of peanut allergen powder-dnfp (Palforzia) therapy past the age of 17 years. Studies in adults are on-going.
- II. FDA approval of peanut allergen powder-dnfp (Palforzia) in patients aged 1 to <4 years old was demonstrated in the pivotal Phase 3 double-blind, placebo-controlled trial (POSEIDON) in July 2024. A total of 146 subjects aged 1 to <4 years old with peanut allergy were included in the trial. In the POSEIDON trial, the prespecified primary efficacy population consisted of 98 subjects aged 1 to <4 years who received at least one dose of Palforzia, while 48 participants received placebo. The primary endpoint was the ability to tolerate a single dose of ≥600 mg of peanut protein with no more than mild allergic symptoms, defined by pruritus, swelling or rash, abdominal discomfort, or other transient or mild discomforts (<48 hours), and no or minimal

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medical intervention/therapy required. Most adverse events in the Palforzia group were mild to moderate in severity, primarily consisting of gastrointestinal symptoms. A total of 86.7% of participants in the Palforzia group were able to tolerate the single 600 mg dose of peanut protein during the exit double-blind placebo-controlled food challenge (DBPCFC), compared to 6.7% in the placebo group. This reflects a treatment difference of 80.1% and indicates a statistically and clinically significant improvement in desensitization in this age group.

- III. In the PALISADE and POSEIDON trial, subjects had confirmed peanut allergy diagnosis consisting of a clinical history of peanut allergy and an elevated IgE test (≥ 0.35 kUA/L) or positive skin test (mean wheal diameter ≥ 3 mm larger than negative control). To be included in the trial subjects must have also had a reaction to an oral food challenge with dose limiting symptoms to no more than 100 mg of peanut protein (roughly one third of a peanut kernel). Oral food challenges are not routinely done in practice but may be needed if the patient's clinical history and IgE test results do not clearly indicate an allergy.
- IV. A confirmed allergy diagnosis consisting of a clinical history of allergy along with confirmatory values (elevated IgE, positive skin test, or food challenge) is utilized as per guideline recommendations. The 2010 Guidelines for the Diagnosis and Management of Food Allergy in the United States indicate, "because individuals can develop allergic sensitization (as evidenced by the presence of allergen-specific IgE (sIgE)) to food allergens without having clinical symptoms on exposure to those foods, an sIgE-mediated food allergy requires both the presence of sensitization and the development of specific signs and symptoms on exposure to that food. Sensitization alone is not sufficient to define food allergy".
- V. The peanut allergen powder-dnfp (Palforzia) package insert and Risk Evaluation and Mitigation Strategy (REMS) program requires peanut allergen powder-dnfp (Palforzia) to be used in conjunction with a peanut-avoidant diet and prescribed with injectable epinephrine. Additionally, the package insert carries a black box warning for anaphylaxis that further states treatment should not be administered in patients with uncontrolled asthma.
- VI. Peanut allergen powder-dnfp (Palforzia) carries a warning and precaution for eosinophilic esophagitis as cases of eosinophilic esophagitis occurred in clinical trials (13.7% of patients during dose escalation). Use in patients with a history of eosinophilic esophagitis is contraindicated per the package insert. Eosinophilic esophagitis is inflammation and increased numbers of eosinophils in the esophagus. It can cause feeding disorders, vomiting, reflux symptoms, abdominal pain in children; and dysphagia and esophageal food impactions in adolescents and adults. Eosinophilic esophagitis is a known complication of oral immunotherapy.
- VII. Viaskin™ Peanut patch is a peanut desensitization therapy under review by the FDA. Safety and efficacy of combination use of peanut desensitization therapy is unknown.
- VIII. An evidence report by the Institute for Clinical and Economic Review (ICER) states there is only moderate certainty of a comparable, small, or substantial net health benefit and a small (but non-zero) likelihood of a negative net health benefit for peanut allergen powder-dnfp (Palforzia) compared with strict avoidance and rapid use of epinephrine (PI, promising, but inconclusive). This is due to net health benefit being driven by changes in quality of life and reductions in reactions to accidental exposure to peanuts, neither of which has been demonstrated. Additionally, the increase in patients treated who were able to tolerate 600 mg of peanut protein (~2 peanut kernels) during the exit food challenge in the trial compared with those

treated with placebo (67.2% vs. 4.0%) is balanced by a significant increase in gastrointestinal symptoms, systemic allergic reactions, and epinephrine use.

- IX. Use of peanut allergen powder-dnfp (Palforzia) is reserved for members with a history of severe peanut allergy. Due to the safety risks noted above coupled with the unknown clinical significance and meaningfulness of improving tolerance of a single dose of 600 mg peanut protein. How tolerance of 600 mg of peanut protein relates to changes in quality of life and reductions in reactions to accidental exposure to peanuts was not evaluated in the clinical trial.

Investigational or Not Medically Necessary Uses

- I. Peanut allergen powder-dnfp (Palforzia) has not been FDA-approved, or sufficiently studied for safety and efficacy for the conditions or settings listed below:
- A. Initial dose escalation in members 18 years of age and older
- i. Though the PALISADE trial included subjects aged 4-55 years, the prespecified primary analysis population consisted of the subjects aged 4-17 years (and subsequently in subjects aged 1 to <4 years old in the POSEIDON trial) who received at least one dose of study drug (n=496). Efficacy in those who were 18 and older (n=55) was evaluated as a secondary endpoint but did not show statistical significance.
- ii. FDA-approval is specific to patients aged 1 through 17 years, although Up-Dosing and Maintenance may be continued in patients 1 years of age and older. To date, there is insufficient evidence to support the initiation of peanut allergen powder-dnfp (Palforzia) therapy past the age of 17 years. Studies in adults are on-going.

References

1. Palforzia [Prescribing information]. Aimmune Therapeutics, Inc: Brisbane, CA. January 2020.
2. Vickery BP, Vereda A, Casale TB, et al. AR101 Oral Immunotherapy for Peanut Allergy. *N Engl J Med*. 2018;379(21):1991-2001.
3. Sampson HA, Aceves S, Bock SA, et al. Food allergy: a practice parameter update-2014. *J Allergy Clin Immunol*. 2014;134(5):1016-25.e43.
4. UpToDate, Inc. Investigational therapies for food allergy: Oral immunotherapy. UpToDate [database online]. Waltham, MA. Last updated Nov 25, 2019 Available at: <http://www.uptodate.com/home/index.html>.
5. UpToDate, Inc. Diagnostic evaluation of food allergy. UpToDate [database online]. Waltham, MA. Last updated Apr 23, 2019 Available at: <http://www.uptodate.com/home/index.html>.
6. Boyce JA, Assa'ad A, Burks AW, et al; NIAID-Sponsored Expert Panel. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol*. 2010;126(suppl 6):S1-S58. doi: 10.1016/j.jaci.2010.10.007
7. Sampson HA, Gerth van wijk R, Bindslev-jensen C, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. *J Allergy Clin Immunol*. 2012;130(6):1260-74.
8. Institute for Clinical and Economic Review. Oral immunotherapy and Viaskin peanut for peanut allergy: Effectiveness and value. Published July 20, 2019. Available at: <https://icer-review.org/material/peanut-allergy-final-evidence-report-and-meeting-summary>.
9. brown kari. Oral immunotherapy for peanut allergy in children 1 to less than 4 years of age. *NEJM Evidence*.
10. Palforzia (Level 5) Oral: Uses, Side Effects, Interactions, Pictures, Warnings & Dosing - WebMD. Webmd.com. Published 2025. Accessed June 9, 2025. <https://www.webmd.com/drugs/2/drug-178768/palforzia-level-5-oral/details>
11. Learning Early About Peanut Allergy (LEAP) - FoodAllergy.org. www.foodallergy.org. <https://www.foodallergy.org/resources/learning-early-about-peanut-allergy-leap>

12. Borne GE, Daniel CP, Wagner MJ, et al. Palforzia for Peanut Allergy: A Narrative Review and Update on a Novel Immunotherapy. *Cureus*. 2023;15(12):e50485. Published 2023 Dec 13. doi:10.7759/cureus.50485
13. Jones SM, Kim EH, Nadeau KC, et al. Efficacy and safety of oral immunotherapy in children aged 1-3 years with peanut allergy (the Immune Tolerance Network IMPACT trial): a randomised placebo-controlled study. *Lancet*. 2022;399(10322):359-371. doi:10.1016/S0140-6736(21)02390-4
14. Skolnick HS, Conover-Walker MK, Koerner CB, Sampson HA, Burks W, Wood RA. The natural history of peanut allergy. *J Allergy Clin Immunol*. 2001;107(2):367-374. doi:10.1067/mai.2001.112129
15. Addendum Guidelines for the Prevention of Peanut Allergy in the United States Report of the NIAID-Sponsored Expert Panel. <https://www.niaid.nih.gov/sites/default/files/addendum-peanut-allergy-prevention-guidelines.pdf>

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated criteria to allow treatment of peanut allergy in patients 1 to <4 years of age given age expansion. Updated supporting evidence and E/I age limits.	06/2025
Policy created	05/2020

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP098

Description

Peginterferon alfa-2b (Sylatron) is a subcutaneous interferon which induces cellular activities related to binding specific cell-surface membrane receptors. These include suppression of cell proliferation, antiviral activity and immunomodulating effects.

Length of Authorization

- Initial: Eight weeks
- Renewal: 12 months, maximum of five years of therapy

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
peginterferon-alfa 2b (Sylatron)	200 mcg subcutaneous powder for solution	Adjuvant treatment of melanoma with microscopic or gross nodal involvement	4 vials/ 28 days
	300 mcg subcutaneous powder for solution		
	600 mcg subcutaneous powder for solution		

Initial Evaluation

- I. Peginterferon alfa-2b (Sylatron) 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. A diagnosis of **melanoma** when the following are met:
 1. The member has stage III disease; **AND**
 2. The member has microscopic or gross nodal involvement; **AND**
 3. The member has had definitive surgical resection including complete lymphadenectomy within the past 84 days (12 weeks); **AND**
 4. Peginterferon alfa-2b is prescribed as adjuvant treatment; **AND**
 5. The prescribed dose does not exceed 6 mcg/kg per week for the first eight weeks, then 3 mcg/kg per week thereafter; **AND**
 6. Attestation from the provider that the member does **not** have any of the following:
 - i. Hepatic decompensation (Child-Pugh Score >6, class B and C)
 - ii. Autoimmune hepatitis

iii. Depression or other neuropsychiatric disorders

- II. Peginterferon-alfa 2b (Sylatron) is considered investigational when used for all other conditions, including but not limited to:
- A. Hepatitis C
 - B. Cholangiocarcinoma
 - C. Hematological malignancies
 - D. Solid tumors and malignancies outside of melanoma

Renewal Evaluation

- I. Member has not been established on therapy by the use of free samples, manufacturer coupons, or otherwise; **AND**
- II. Member has received a previous prior authorization approval for this agent; **AND**
- III. The medication is prescribed by or in consultation with an oncologist; **AND**
- IV. Member has experienced response to treatment, such as stabilization of disease, decrease in disease spread, regression of disease; **AND**
- V. The prescribed dose does not exceed 3 mcg/kg after the first eight weeks of therapy; **AND**
- VI. Attestation from the provider that the member does not have any of the following:
 - Hepatic decompensation (Child-Pugh Score >6, class B and C)
 - Autoimmune hepatitis
 - Depression or other neuropsychiatric disorders

Supporting Evidence

- I. Peginterferon-alfa 2b (Sylatron) was evaluated in an open-label, randomized study of 1256 subjects with surgically resected stage III melanoma within 84 days (12 weeks) of regional lymph node dissection. The dose administered was 6 mcg/kg per week for eight weeks on average. Less than 1% received this dose for longer than nine weeks; thus, safety and efficacy for this dose for more than eight weeks is not FDA-approved and has not been sufficiently evaluated for safety and or efficacy.
- II. Subjects were randomized to observation or peginterferon-alfa 2b (Sylatron) for up to five years. The primary outcome was relapse-free survival (RFS) or death from any cause, with overall survival (OS) as the secondary outcome. The RFS duration for peginterferon-alfa 2b (Sylatron) was 34.8 months versus 25.5 months for the observation arm. Safety and efficacy past five years of therapy has not been established, and OS benefits have not been established.
- III. Peginterferon-alfa 2b (Sylatron) has a Black Box Warning for neuropsychiatric disorders, and may cause or aggravate severe depression or other psychiatric adverse events. Members with these conditions should only be started on therapy if the benefit outweighs the risks and should be monitored closely. Resolution of symptoms does not always occur upon discontinuation. Additionally, peginterferon-alfa 2b (Sylatron) is contraindicated in autoimmune hepatitis and those with hepatic decompensation.

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- IV. Vials of peginterferon-alfa 2b (Sylatron) are dose priced; therefore, vial size should be chosen to provide the appropriate dose and minimize waste.
- V. As of November 2019, National Comprehensive Cancer Network treatment guidelines for cutaneous melanoma did not have recommendations for peginterferon-alfa 2b (Sylatron) in the setting of melanoma.

Investigational or Not Medically Necessary Uses

- I. Peginterferon-alfa 2b (Sylatron) is not FDA-approved and has not been sufficiently evaluated for safety and/or efficacy in the following settings:
 - A. Hepatitis C
 - B. Cholangiocarcinoma
 - C. Hematological malignancies
 - D. Solid tumors and malignancies outside of melanoma

References

1. Sylatron [Prescribing Information]. Merck Sharp & Dohme Corp. Whitehouse Station, NJ. 2011.
2. NCCN Clinical Practice Guidelines in Oncology Cutaneous Melanoma. V3.2019. National Comprehensive Cancer Network. October 22, 2019. Available at: https://www.nccn.org/professionals/physician_gls/default.aspx#melanoma.

Policy Implementation/Update:

Date Created	December 2012
Date Effective	January 2013
Last Updated	November 2019
Last Reviewed	11/2019

Action and Summary of Changes	Date
Prior authorization criteria transitioned to policy format. Criteria updated to include age edit, stage of disease, place in therapy, maximum dose. Renewal criteria updated to current format and language, added specialist requirement, contraindications, dose check. Change of initial duration of approval, change to maximum coverage of five years.	11/2019

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP213

Description

Peginterferon alfa-2a (Pegasys) is a subcutaneous pegylated interferon which induces cellular activities related to binding specific cell-surface membrane receptors. These include suppression of cell proliferation, antiviral activity, and immunomodulating effects.

Length of Authorization

- Initial:
 - Chronic Hepatitis B: 48 weeks
 - All other indications: 12 months
- Renewal:
 - i. For Polycythemia Vera AND Essential Thrombocythemia: 12 months
 - ii. For all other indications: None

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
Peginterferon Alfa-2a (Pegasys; Pegasys ProClick)	180 µg/mL vial	Chronic Hepatitis B; Chronic Hepatitis D; Polycythemia Vera; Essential Thrombocythemia	4 vials/30 days
	180 µg/0.5 mL prefilled syringe		4 syringes/30 days
	135 µg/0.5 mL autoinjector		4 autoinjectors/30 days
	180 µg/0.5 mL autoinjector		4 autoinjectors/30 days

Initial Evaluation

- I. **Peginterferon Alfa-2a (Pegasys)** may be considered medically necessary when the following criteria below are met:
 - A. The medication is prescribed by, or in consultation with, a gastroenterologist, hepatologist, infectious disease specialist, hematologist, or an oncologist; **AND**
 - B. The medication will be used as monotherapy; **AND**
 - C. Member has not previously experienced disease progression while on peginterferon Alfa-2a (Pegasys) for the treatment of indications listed in this policy; **AND**
 - D. Provider attestation that the member does **not** have any of the following:
 - i. Hepatic decompensation (Child-Pugh Score > 6, Class B and C)
 - ii. Autoimmune hepatitis
 - iii. Depression or other neuropsychiatric disorders; **AND**
 - E. A diagnosis of one of the following:
 1. **Chronic Hepatitis B; AND**
 - i. Member is 3 to 17 years old; **AND**

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- a. Provider attests to **ALL** of the following:
 - i. Member is hepatitis B e-antigen (HBeAg) positive; **AND**
 - ii. Member is noncirrhotic; **AND**
 - iii. Member has elevated serum alanine aminotransferase (ALT) more than twice the upper limit of normal (ULN);**OR**
 - ii. Member is 18 years of age or older; **AND**
 - a. Documentation of hepatitis B (HBV) viral load less than 12 months old (i.e. serum HBV > 100,000 copies/mL or HBV DNA levels > 2000 IU/mL); **OR**
 - 2. **Chronic Hepatitis D; AND**
 - i. Diagnosis of chronic hepatitis D (HDV) confirmed by a quantifiable HDV RNA; **AND**
 - ii. Provider attests the member has active liver disease (e.g. elevated serum ALT, or liver biopsy); **OR**
 - 3. **Polycythemia Vera; OR Essential Thrombocythemia; AND**
 - i. Member is 18 years of age or older; **AND**
 - ii. Provider attests that the member has high-risk disease; **AND**
 - iii. Treatment with generic hydroxyurea has been ineffective, contraindicated, or not tolerated
- II. Peginterferon Alfa-2a (Pegasys) is considered not medically necessary when used for:
 - A. Treatment of chronic hepatitis C (HCV)
- III. Peginterferon Alfa-2a (Pegasys) is considered investigational when used for all other conditions, including but not limited to:
 - A. Malignant melanoma
 - B. Renal cell carcinoma
 - C. Hairy cell leukemia
 - D. Myelofibrosis
 - E. Systemic mastocytosis
 - F. Chronic myelogenous leukemia (CML)

Renewal Evaluation

- I. Member has not been established on therapy by use of free samples, manufacturer coupons or otherwise; **AND**
- II. Member has received previous prior authorization for this agent through THIS health plan; **AND**
- III. Provider attestation that the member does **not** have any of the following:
 - i. Hepatic decompensation (Child-Pugh Score > 6, Class B and C)
 - ii. Autoimmune hepatitis
 - iii. Depression or other neuropsychiatric disorders; **AND**
- IV. Member has diagnosis of **Polycythemia Vera, or Essential Thrombocythemia; AND**

- V. Member has experienced response to therapy such as disease stabilization or remission (e.g. complete or partial response)

Supporting Evidence

- I. Interferons, a family of naturally occurring small protein molecules or glycoproteins, are produced by cells in response to viral infections or various synthetic or biologic inducers. Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Once bound to the cell membrane, interferons initiate a complex sequence of intracellular events. Interferons have been found to mediate antiviral, antiproliferative, and immunomodulatory activities. Peginterferon alfa-2a (Pegasys®) is a covalent conjugate of recombinant alfa-2a interferon. Other types of alfa interferon such as Peginterferon alfa-2b (PegIntron®, Sylatron™) are covered under separate PA policies based on their respective indications.
- II. Given the treatment complexities associated with the indications listed in this policy, use of peginterferon alfa-2a (Pegasys) should be prescribed by a specialist practicing in the respective area of specialty.
- III. Patients with chronic hepatitis B are at an increased risk to develop cirrhosis, liver failure, and liver cancer. Hepatitis B e-antigen (HBeAg) and Hepatitis B viral DNA (HBV DNA) are both markers of HBV replication and their presence provides a rationale for initiating therapy to stop the progression of liver disease. In the past, the ability to detect HBV DNA in the serum by hybridization assays was a major factor in determining which patients should be treated. This assay is sensitive enough to detect viral DNA when it is present in amounts ≥ 105 copies/ml and consequently this viral level became an important benchmark in treatment algorithms. As improvements in viral detection have advanced it has become apparent that it is not possible to designate a single HBV DNA value that can differentiate between inactive hepatitis B carriers and patients suffering from chronic hepatitis B.
- IV. There are several agents currently indicated for treatment of chronic HBV. They include Peginterferon, lamivudine, telbivudine, entecavir, tenofovir and adefovir. AASLD guidelines recommend peginterferon alfa-2a, entecavir, or tenofovir as preferred initial therapy for adults with immune-active chronic HBV infection. peginterferon alfa-2b is not FDA approved for chronic hepatitis B; however, there are studies that support its use for this indication. Overall, the quality of evidence is considered low for this setting.
- V. Interferon therapy is not recommended in patients with decompensated cirrhosis because it increases their risk for developing bacterial infections and it can potentially worsen their condition.
- VI. Peginterferon alfa-2a (Pegasys) was evaluated in multiple phase 3, randomized clinical trials, as monotherapy and in combination with lamivudine, for patients with HBV infection. All subjects were adults with compensated liver disease, had chronic HBV infection and evidence of HBV replication (serum HBV greater than 500,000 copies/mL for HBeAg-positive patients and greater than 100,000 copies/mL for HBeAg-negative patients). All subjects had serum ALT between 1 and 10 times the upper limit of normal (ULN). Treatment with peginterferon alfa-2a (Pegasys) exhibited significant serological, virological, and histological responses at the treatment interval of 24 weeks. Co-administration of lamivudine with Pegasys did not result in additional sustained response as compared to Pegasys monotherapy.
- VII. In the setting of chronic hepatitis C (HCV), the sustained virological response (SVR) is defined as undetectable HCV RNA in 12 weeks (SVR 12) or 24 weeks (SVR 24) after treatment completion.

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Cure rate, which achieves SVR, is more than 99%. SVR is generally associated with resolution of liver disease in patient without cirrhosis, but in the patient with cirrhosis there remains risk of life-threatening complications.

- VIII. Peginterferon alfa-2a (Pegasys) has been studied as monotherapy and in combination with ribavirin in seven randomized, active-controlled clinical trials. Pooled population analysis showed the participants in these trials had HCV genotype 1 through 6, were of ages 5 years and above, and had detectable viral load at treatment initiation. Therapeutic responses were observed at median 12 weeks of treatment and durability of response sustained up to the 48-week trial window. Recommended total duration of therapy for peginterferon alfa-2a (Pegasys) is up to 48 weeks (per FDA-approval).
- IX. The only guideline recommended treatment of chronic hepatitis D is interferon alfa (IFN- α). Peginterferon alfa is the drug of choice without clear differences in efficacy between peginterferon alfa-2a (Pegasys) or peginterferon alfa-2b (Pegintron). Treatment success, defined as undetectable HDV RNA at 24 weeks after completing treatment, ranges from 23% to 57%. Late relapses can occur with longer follow-up, leading to very low rates of sustained HDV-RNA undetectability. In the multicenter HIDIT-1 (Hep-Net-International-Delta-Hepatitis-Intervention-Study 1) study of peginterferon alfa-2a (Pegasys) for 48 weeks with or without adefovir, 40% of patients achieved an undetectable HDV-RNA level 24 weeks after completing therapy, but at a mean follow-up 4.3 years later, only 12% remained undetectable.
- X. Although not FDA-approved, use of peginterferon alfa-2a (Pegasys) is supported by NCCN guidelines (category 2A recommendation) for the treatment of essential thrombocythemia (ET) and polycythemia vera (PV). PV and ET are BCR-ABL1–negative myeloproliferative neoplasms. Both diseases are characterized by a clonal myeloid proliferation with excessive production of blood elements. The hallmarks of ET and PV include an increased risk of thrombohemorrhagic complications, and a variable risk of transformation to myelofibrosis (MF) and/or acute myeloid leukemia (AML). Recommended use of peginterferon alfa-2a (Pegasys) in these settings is based on multiple clinical trials and retrospective studies. Notably, a phase 2 open-label clinical trial assessed Pegasys for induction of complete (CR) and partial (PR) hematologic responses in patients with high-risk ET (n=65) or PV (n=50), who were either refractory or intolerant to HU. The overall response rates (ORRs; CR/PR) at 12 months were 69.2% (43.1% and 26.2%) in ET patients and 60% (22% and 38%) in PV patients. This clinical trial was further extended to a confirmatory phase 3 trial using hydroxyurea as active comparator (N=168), wherein similar ORR was observed in the treatment arm. The treatment efficacy was comparable to hydroxyurea.
- XI. For PV and ET patient populations, high-risk disease is defined by a history of thrombosis, age >60 years, a history of bleeding (ET only), platelet counts >1500 X 10⁹/L in ET and >1000 X 10⁹/L in PV, vasomotor symptoms (erythromelalgia, severe migraine headaches), significant or symptomatic splenomegaly, and the presence of diabetes or uncontrolled hypertension. However, younger patients (<60 years) without any other defining factors may qualify for cytoreductive therapy with peginterferon alfa-2a (Pegasys) when hydroxyurea is contraindicated (e.g. during pregnancy).
- XII. There is lack of efficacy and safety data for use of peginterferon alfa-2a (Pegasys) in pediatric population with ET and/ or PV.

Investigational or Not Medically Necessary Uses

- I. Peginterferon alfa-2a (Pegasys) has been investigated for safety and efficacy in some the following indications. Safety and efficacy have not been established in all of the following:
 - A. Chronic hepatitis C: Although included as an FDA-approved use in the manufacturer's prescribing information for the treatment of chronic hepatitis C (HCV) infection in compensated liver disease, the WHO and AASLD guidelines no longer recommend interferon-based regimens for HCV infection. Recently updated 2019 AASLD guidelines for treatment of hepatitis C recommend use of newer direct antiviral agents (DAA) as preferred treatment regimens. Overall, it is guideline consensus that peginterferon alfa-2a based treatments have relatively lower efficacy, longer onset of action and higher safety concerns. Therefore, use of peginterferon alfa-2a is recommended for limited situations when all DAA are contraindicated.
 - B. Myelofibrosis: NCCN guideline for myeloproliferative neoplasms recommends use of peginterferon alfa-2a (Pegasys) as 'useful in certain circumstances' as a possible alternative to ruxolitinib (Jakafi) and hydroxyurea, only when cytoreduction is considered symptomatically beneficial. This recommendation stems from a retrospective case study and observational single-center open-label trial in 30 patients, wherein 7% CR and 30% PR were reported. Overall quality of evidence is considered low.
 - C. Systemic mastocytosis: peginterferon alfa-2a (Pegasys) was included in NCCN guidelines for systemic mastocytosis (SM) (category 2A recommendation) as a possible treatment option for advanced SM patients. This recommendation is restricted to patients with slowly progressing disease without need for rapid cytoreduction. Tyrosine kinase inhibitors (TKI), midostaurine (Rydapt), and cladribine remain preferred therapeutic options in this space. Guidelines note that alfa interferon has recently fallen out of favor because of its slow onset of action and poor tolerability. Given the potential harmful effects of kinase inhibitors on germ cells and cladribine on the fetus (both pregnancy category D), alfa interferon may be an option in pregnancy. However, there are no supporting clinical trials to establish the efficacy and safety of peginterferon alfa-2a (Pegasys) in this patient population.
 - D. Chronic myelogenous leukemia (CML): NCCN guidelines recommend use of interferon alfa for management of CML during pregnancy due to contraindication to use of tyrosine kinase inhibitors (TKI) and hydroxyurea in this population. It is noted that if introduced earlier (during 1st trimester), the use of interferon may preserve molecular remission after discontinuation of TKI or HU. However, data are insufficient to establish the use of peginterferon alfa-2a (Pegasys) in pregnancy.
 - E. Renal cell carcinoma (RCC): interferon-alfa was studied in RCC as an adjuvant therapy for high-risk, clear cell, localized RCC post nephrectomy. Randomized trials in patients who had locally advanced, completely resected RCC showed no delay in time to relapse or improvement in survival with adjuvant therapy.
 - F. Malignant melanoma: Interferon alfa-2b (Intron A) and peginterferon alfa-2b (Sylatron) have supporting clinical evidence and are FDA-approved for malignant melanoma. Safety and efficacy of peginterferon alfa-2a (Pegasys) has not been established in these settings.
 - G. Hairy cell leukemia: NCCN guidelines for hairy cell leukemia recommend peginterferon alfa-2a as a possible alternative for the treatment of relapsed/ refractory hairy cell leukemia. However, purine analogs (cladribine, pentostatin) and rituximab remain preferred

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therapeutic options in this space. In a 1995 phase III intergroup study (N=319), efficacy and safety of pentostatin was compared with that of interferon alfa with a treatment follow-up of median 57 months. Subjects receiving Pentostatin reported higher complete remission (CR) rates versus those with interferon alfa treatment (76% vs 11%; $p < 0.0001$) along with longer relapse-free survival (RFS) (not reached vs 20 months; $p < 0.0001$). NCCN guidelines note that with the advent of purine analogs, the role of interferon alfa as a treatment option for hairy cell leukemia is limited.

References

1. Pegasys (peginterferon alfa-2a) [prescribing information]. South San Francisco, CA: Genentech Inc; October 2020.
2. Abbas Z, Memon MS, Mithani H, Jafri W, Hamid S. Treatment of chronic hepatitis D patients with pegylated interferon: a real-world experience. *Antivir Ther*. 2014;19(5):463-8.
3. Hepatitis C Guidance 2018 Update: AASLD-IDS Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection; <https://www.aasld.org/publications/practice-guidelines>
4. Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance; 2018, hematology; 67 (4), 1560. <https://www.aasld.org/publications/practice-guidelines>.
5. World Health Organization Guidelines For The Care And Treatment of Persons Diagnosed With Chronic Hepatitis C Virus Infection. 2018; <https://apps.who.int/iris/bitstream/handle/10665/273174/9789241550345-eng.pdf?ua=1>
6. Yacoub A, Mascarenhas J, et al.; Pegylated interferon alfa-2a for polycythemia vera or essential thrombocythemia resistant or intolerant to hydroxyurea. *Blood*. 2019 Oct 31;134(18):1498-1509.
7. U.S. National Library of Medicine; Clinical Trials database; NCT01259856; NCT00452023; NCT00241241; <https://clinicaltrials.gov>.
8. Heidrich B, Yurdaydin C, Kabaçam G, Ratsch BA, Zachou K, Bremer B, Dalekos GN, Erhardt A, Tabak F, Yalcin K, Gürel S, Zeuzem S, Cornberg M, Bock CT, Manns MP, Wedemeyer H; HIDI-1 Study Group. Late HDV RNA relapse after peginterferon alpha-based therapy of chronic hepatitis delta. *Hepatology*. 2014 Jul;60(1):87-97.

Policy Implementation/Update:

Action and Summary of Changes	Date
Criteria update: Transition from criteria to policy format and review of FDA-approved and guideline supported indications for peginterferon alfa-2a (Pegasys). Added supporting evidence for all indications listed in the policy. Removed indication of chronic hepatitis C per current AALSD and WHO guideline recommendation. Reviewed available evidence for indications listed under not medically necessary and investigational uses and added relevant clinical information to supporting evidence section	12/2020
Previous reviews and updates	12/2012; 08/2012; 12/2011; 12/2008; 11/2007
Criteria created	01/2006

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP149

Description

Pegvisomant (Somavert) selectively binds to growth hormone (GH) receptors on cell surfaces, where it blocks the binding of endogenous GH, and thus interferes with signal transduction. Inhibition of GH action results in decreased serum concentrations of insulin-like growth factor-I (IGF-I), as well as other GH-responsive serum proteins, including IGF binding protein-3 (IGFBP-3), and the acid-labile subunit (ALS).

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity Limits

Product Name	Dosage Form	Indication	Quantity Limit
pegvisomant (Somavert)	10 mg vial	Acromegaly	60 vials/30 days
	15 mg vial		60 vials/30 days
	20 mg vial		30 vials/30 days
	25 mg vial		30 vials/30 days
	30 mg vial		30 vials/30 days

Initial Evaluation

- I. Pegvisomant (Somavert) 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; **AND**
 - C. A diagnosis of **acromegaly** when the following are met:
 1. Diagnosis is confirmed by elevated serum IGF-1 for member's age and gender, (including laboratory reference range); **OR**
 - a. If normal IGF-1, elevated growth hormone level nadir of > 1 ng/mL during an oral glucose tolerance test (OGTT); **AND**
 2. Documentation of inadequate response to surgery or radiation therapy; **AND**
 3. Treatment with octreotide (Sandostatin), cabergoline, or bromocriptine (Parlodel) has been ineffective, contraindicated, or not tolerated
- II. Pegvisomant (Somavert) 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 (improvements in sleep apnea, tissue swelling, headache, arthralgias); **AND**
- IV. Serum IGF-1 level has decreased from baseline or normalized (according to the lab reference range based on member age and gender)

Supporting Evidence

- I. Acromegaly is a hormonal disorder that occurs when the pituitary gland produces too much growth hormone (GH). Typically, this is caused by adenomas (benign tumor) on the pituitary gland. Diagnosis typically occurs in middle-aged adults; however, symptoms can appear at any age. Surgical intervention is the preferred treatment.
- II. According to the American Association of Clinical Endocrinologists (AACE) guidelines, medical therapy is pursued in patients with a tumor that cannot be completely removed surgically, have no compressive tumor effects, are poor surgical candidates, or prefer medical management. Goals of therapy include the normalization of biochemical variables, reversal of mass-effects of the tumor, improvement in signs, symptoms, and comorbidities of disease, and the minimization of long-term mortality risk. In most patients, medical therapy is used as adjuvant treatment in the setting of persistent disease despite surgical intervention.
- III. AACE guidelines recommend a random IGF-1 value (a marker of integrated GH secretion) to be measured for diagnosis and as post-intervention therapeutic monitoring. A serum IGF-1 level should be remeasured at 12 weeks; a normal IGF-1 value is consistent with surgical remission. If a repeat serum IGF-1 value is reduced from baseline, but is still elevated at 12 weeks, an additional repeat testing is done in another 9 to 12 weeks to determine the presence of delayed biochemical normalization, before proceeding with potential surgical re-exploration, medical therapy, or radiation therapy. Additionally, an oral glucose tolerance test is also utilized as a diagnostic tool, especially in conditions that are associated with lower IGF-1 concentrations (e.g., hypothyroidism, malnutrition, uncontrolled type 1 diabetes, liver failure, renal failure, oral estrogen use) where the diagnosis of acromegaly could be missed. Inability to suppress serum GH to less than 1 ng/mL after glucose administration is considered the diagnostic criterion for acromegaly and is the gold standard for determining control of GH secretion after surgical treatment.
- IV. Per guidelines, there are three classes of medical therapy: dopamine agonists (e.g. caberfoline, bromocriptine), somatostatin analogues (e.g. octreotide, lanreotide), and a GH-receptor antagonist (e.g. pegvisomant). Dopamine agonists are considered first-line medical therapy as they are relatively inexpensive in comparison to alternative medical therapy options and have simple oral administration.
- V. With the administration of pegvisomant (Somavert), serum IGF-1 should be measured alone to monitor the dose efficacy. There is no benefit from the measurement of serum GH in

conjunction with pegvisomant (Somavert) therapy. GH levels increase when pegvisomant (Somavert) is administered, and the GH levels have no effect on pegvisomant (Somavert) dosing.

Investigational or Not Medically Necessary Uses

- I. There is limited to no evidence to support the use of pegvisomant (Somavert) in any other condition.

References

1. Somavert [Prescribing Information]. New York, NY: Pfizer; September 2019.
2. UpToDate, Inc. Treatment of acromegaly. UpToDate [database online]. Waltham, MA. Last updated August 20, 2019 Available at: <http://www.uptodate.com/home/index.html>.
3. UpToDate, Inc. Diagnosis of acromegaly. UpToDate [database online]. Waltham, MA. Last updated August 26, 2019 Available at: <http://www.uptodate.com/home/index.html>.
4. Katznelson L, Atkinson JL, Cook DM, et al. American Association of Clinical Endocrinologists. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of acromegaly--2011 update. Endocr Pract. 2011 Jul-Aug;17(Suppl 4):1-44.

Policy Implementation/Update:

Action and Summary of Changes	Date
Addition of confirmed diagnosis requirements (elevated IGF-1 or GH level). Added requirement of reduced or normalized IGF-1 levels at renewal. Updated initial approval duration from 12 months to 6 months.	05/2020
Addition of renewal criteria. Added age requirement of 18 years or older. Added requirement for agent to be prescribed by or in consultation with an endocrinologist.	12/2019
Policy created	01/2006

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP085

Split Fill Management* (Only Applies to pexidartinib (Turalio))

Description

Pexidartinib (Turalio) and vimseltinib (Romvimza) are oral kinase inhibitors.

Length of Authorization

- Initial: Six months, split fill for the first three months for pexidartinib (Turalio)
- Renewal: 12 months

Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit
pexidartinib (Turalio)	125 mg capsule	Tenosynovial giant cell tumor (TGCT) associated with severe morbidity or functional limitations and not amenable to improvement with surgery	120 capsules/30 days
Vimseltinib (Romvimza)	14 mg capsules	Tenosynovial giant cell tumor (TGCT) for which surgical resection will potentially cause worsening functional limitation or severe morbidity	8 capsules/28 days
	20 mg capsules		
	30 mg capsules		

Initial Evaluation

- I. **Pexidartinib (Turalio) and vimseltinib (Romvimza)** 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, an oncologist or orthopedic surgeon; **AND**
 - C. Medications in this policy will not be used in combination with other tyrosine kinase inhibitors that also target colony-stimulating factor (CSF1) or the CSF1 receptor (CSF1R) (e.g., imatinib, nilotinib, sorafenib, or sunitinib); **AND**
 - D. Member has a confirmed diagnosis of **symptomatic tenosynovial giant cell tumor (TGCT)**; **AND**
 1. Diagnosis is confirmed via biopsy; **OR**
 - i. Diagnosis is confirmed via imaging (e.g., magnetic resonance imaging (MRI), radiographs, ultrasonography, etc.); **AND**
 2. Provider attestation member has symptomatic disease with at least moderate pain or stiffness; **AND**
 - E. Provider attests member is not a candidate for surgery (i.e., surgical resection will potentially cause worsening functional limitation or severe morbidity); **AND**

- F. The medication is used as a monotherapy; **AND**
 - G. If the request is for pexidartinib (Turalio): Member does not have preexisting increased serum transaminases such as ALT and AST or an indication of hepatotoxicity; **AND**
 - 1. Member has not previously progressed on vimseltinib (Romvimza); **OR**
 - H. If the request is for vimseltinib (Romvimza): Member has not previously progressed on pexidartinib (Turalio).
- II. Pexidartinib (Turalio) and vimseltinib (Romvimza) are considered investigational when used for all other conditions, including but not limited to:
- A. Metastatic tenosynovial giant cell tumor (TGCT)
 - B. Active cancer that requires therapy (e.g. surgical, chemotherapy, or radiation therapy)
 - C. Used in combination with other tyrosine kinase inhibitors that also target colony-stimulating factor (CSF1) or the CSF1 receptor (CSF1R) (e.g., imatinib, nilotinib, sorafenib, or sunitinib)

Renewal Evaluation

- A. 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**
- B. 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**
- C. Medications in this policy will not be used in combination with other tyrosine kinase inhibitors that also target colony-stimulating factor (CSF1) or the CSF1 receptor (CSF1R) (e.g., imatinib, nilotinib, sorafenib, or sunitinib); **AND**
- D. Disease response to treatment defined by stabilization of disease or decrease in tumor size or spread (i.e., stable or improved range of motion of affected joint, stable or improved pain in affected joint, stable or improved in stiffness of affected joint, etc.); **AND**
- E. Member has not experienced disease progression on pexidartinib (Turalio) and/or vimseltinib (Romvimza)

Supporting Evidence

- I. Historically known as giant cell tumor of the tendon sheath (GCTTS) or pigmented villonodular synovitis (PVNS), tenosynovial giant cell tumor (TGCT) is a slow-growing, locally invasive tumor of the synovium that is usually benign. It is thought to be caused by overexpression of the CSF1 gene which leads to the growth and expansion of tumors by recruiting and inducing local proliferation of CSF1R-dependent inflammatory cells. TGCT can cause debilitating symptoms including pain, stiffness, restricted mobility, and joint damage. TGCT almost always involves a single joint with the knee and foot synovial structures, while involvement of the shoulder, wrist/hand, and hip is less common. It is estimated there is a total population of 9000 patients in the United States, and although TGCT can affect individuals of all ages, it most commonly occurs in adults between 25 and 50 years of age and is more common in women than in men.
- II. Diagnosis of TGCT is often delayed or misdiagnosed due to many presenting with of non-specific TGCT symptoms (e.g., pain and swelling) and patients often see multiple healthcare providers. A confirmed diagnosis of TGCT is established via biopsy or imaging, which may include

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radiographs, ultrasound, or magnetic resonance imaging (MRI). Surgery is the primary treatment option for TGCT, and patients with recurrent and/or relapsed TGCT may typically undergo several surgical interventions. Not all TGCT is amenable to surgery, depending on the tumor size, location, and complexity. If further surgery would result in significant morbidity or functional impairment, systemic therapy are considered as a second-line treatment option.

- III. Before 2019, patients were treated with off-label use of TKI inhibitors, such as imatinib and/or nilotinib. Pexidartinib (Turalio) was first FDA-approved in 2019 for the treatment of adult patients with symptomatic TGCT associated with severe morbidity or functional limitations and not amenable to improvement with surgery. Vimseltinib (Romvimza) is the second kinase inhibitor for the treatment of TGCT to enter the market following pexidartinib (Turalio), for the treatment of adults with symptomatic TGCT associated with severe morbidity or functional limitations and that is not responsive to improvement with surgery. The National Comprehensive Cancer Network (NCCN) Soft Tissue Sarcoma clinical practice guidelines include pexidartinib (Turalio) and vimseltinib (Romvimza) as Category 1 systemic therapy options for TGCT. Imatinib (Gleevec) and nilotinib (Tasigna) are recommended as category 2A under useful in certain circumstances.
- IV. Pexidartinib (Turalio) was studied in the ENLIVEN clinical trial with two parts:
- Part 1: A randomized, double-blind, multicenter, Phase 3 study (n=120) patients with symptomatic advanced TGCT for whom surgical removal of the tumor would be associated with potentially worsening functional limitation or severe morbidity. The primary efficacy outcome in Part 1 was overall response rate (ORR): 39% (24 of 61) with pexidartinib (Turalio) vs. 0% with placebo at week 25 ($p<0.0001$); 53% at data cutoff.
 - Part 2: An open-label, Phase 3 trial for patients (n=78; 30 from the placebo group) who completed the part 1, evaluating ORR of the patients on the crossover treatment. The primary efficacy outcome in Part 2 was ORR: 30% (9 of 30) at week 25; 53% (16 of 30) at data cutoff.
- V. Common adverse events (>20%) in the clinical trial were: hair color change (67%), fatigue (54%), AST increase (39%), nausea (38%), ALT increase (28%), and dysgeusia (25%). Most common grade 3 or 4 adverse events occurring at a higher incidence in patients treated with pexidartinib (Turalio) were increases in liver enzymes. Hepatic adverse events were also the most common cause of treatment interruption, dose reduction (38% combined), or treatment discontinuation (13%) in the pexidartinib (Turalio) group. Pexidartinib (Turalio) has boxed warnings and REMS program for the risk of serious and potentially fatal liver injury and embryo-fetal toxicity.
- VI. Vimseltinib (Romvimza) is used to treat adults with symptomatic TGCT when surgery may make the symptoms worse or cause severe problems. Vimseltinib (Romvimza) is available as an oral 30mg capsule taken twice weekly with ≥ 72 hours between treatment doses. If unable to tolerate 30mg, dose reductions to 20mg and/or 14mg twice weekly dosing is recommended. If unable to tolerate 14 mg twice weekly, it is recommended to permanently discontinue vimseltinib (Romvimza).
- VII. Vimseltinib (Romvimza) was studied in the Phase 3 MOTION trial (NCT05059262), which enrolled 123 patients with TGCT for which surgical resection would potentially cause worsening functional limitations or severe morbidity. All patients were required to have symptomatic disease with at least moderate pain or stiffness and excluded those who had no prior anti-CSF1/CSF1R therapy; however previous use of imatinib and/or nilotinib was allowed.

Participants were randomly assigned (2:1) to receive vimseltinib (Romvimza) 30 mg twice weekly or placebo for 25 weeks (Part 1). At Week 25, patients who completed the double-blind, randomized part of the trial were eligible to advance to an ongoing open-label extension study (Part 2) in which all patients received vimseltinib (Romvimza). Baseline characteristics were similar between both groups: majority of patients had at least 1 previous surgery or procedure (74%), 23% were previously treated with systemic therapy, and the most common disease location was the knee (67%). The primary endpoint of the study was an overall response rate (ORR) per Response Evaluation Criteria In Solid Tumors (RECIST) Version 1.1. at Week 25 versus placebo (ORR was defined as the percentage of participants who achieved either complete response (CR) or partial response (PR)). At Week 25 the overall response rate (ORR) was 40% in the vimseltinib (Romvimza) arm and 0% in the placebo arm ($p < 0.0001$). While the complete response rate is low (5%), the 40% ORR, was driven largely by partial responses (35%), suggests substantial tumor shrinkage and symptom relief. The quality of evidence is considered moderate as vimseltinib (Romvimza) provides a statistically and clinically meaningful benefit for patients with TGCT in patients for whom surgery is not an option. Additionally, 85% of responders maintained their response for at least 6 months, while 58% maintained their response for 9 months or more, indicating durable benefit. Beyond tumor reduction, vimseltinib (Romvimza) met all its secondary endpoints, which significantly improved pain, mobility, and physical function as assessed by patient-reported outcome measures, which are critical for improving the quality of life of patients affected by TGCT-related stiffness and disability.

- VIII. Vimseltinib (Romvimza) was generally well tolerated. The most common adverse reactions ($\geq 20\%$) were increased aspartate aminotransferase (AST), periorbital edema, fatigue, rash, increased cholesterol, peripheral edema, face edema, decreased neutrophils, decreased leukocytes, pruritus, and increased alanine aminotransferase (ALT). Majority of TEAEs were grade mild or moderate severity. TEAEs led to treatment discontinuation in 8% (9/118) of all patients receiving vimseltinib. There are no specific contraindications to using vimseltinib (Romvimza); and while serious and fatal liver injury have not been observed with vimseltinib (Romvimza), the medication carries a warning and precaution for hepatotoxicity, embryo-fetal toxicity, allergic reactions (to tablet ingredients FD&C Yellow No. 5 (tartrazine) and No. 6 (Sunset Yellow FCF), and increased serum creatinine without affecting renal function. Serum enzyme elevations were consistent with the known mechanism of action of CSF1R inhibitors. In contrast to pexidartinib (Turalio), vimseltinib (Romvimza) label does not include a black box warning for hepatotoxicity and it is not subject to a REMS program. While vimseltinib (Romvimza) has not been associated with serious and fatal liver injury, serious and fatal cases of liver injury have occurred with another CSF1R-targeted kinase inhibitor (pexidartinib). There was no evidence of cholestatic hepatotoxicity, drug-induced liver injury, or hair/skin hypopigmentation in the MOTION trial.

Investigational Uses

- I. Metastatic tenosynovial giant cell tumor (TGCT) or Active cancer that requires therapy (e.g. surgical, chemotherapy, or radiation therapy)
 - A. TGCT comprises two clinical distinct subtypes: localized or diffused. Localized lesions have well defined margins that are off-center from or partially/completely envelop tendons mainly affecting the fingers and wrists; while diffuse TGCT impacts larger joints (shoulder,

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knees, hips, ankle, elbows). Metastatic TGCT is a rare condition where the tumor may transform into an aggressive malignant tumor, spreading to other parts of the body. Most cases involve lymph nodes or lung involvement. Patients with known metastatic TGCT or other active cancer that requires concurrent treatment were excluded from the phase 3 MOTION and ENLIVEN clinical trials.

- II. Used in combination with other tyrosine kinase inhibitors that also target colony-stimulating factor (CSF1) or the CSF1 receptor (CSF1R) (e.g., imatinib, nilotinib, sorafenib, or sunitinib)
 - A. Combination use of TKIs for the treatment of TGCT has not been evaluated. Previous therapy with imatinib and/or nilotinib was allowed in the clinical trials, however use of these agents in combination with pexidartinib (Turalio) and vimseltinib (Romvimza) has not been studied and is therefore considered experimental and investigational.

** 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. Turalio [Prescribing Information]. Daiichi Sankyo, Inc. Basking Ridge, NJ. January 2025.
2. Romvimza product dossier. Deciphera Pharmaceuticals. February 2025.
3. Gelderblom H, Bhadri V, Stacchiotti S, et al. Vimseltinib versus placebo for tenosynovial giant cell tumor (MOTION): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2024;403(10445):2709-2719.
4. Tap WD, Gelderblom H, Palmerini E, et al. Pexidartinib versus placebo for advanced tenosynovial giant cell tumour (ENLIVEN): a randomised phase 3 trial. *Lancet*. 2019;394(10197):478-487. doi: 10.1016/S0140-6736(19)30764-0.
5. Scharschmidt, T. (2017). Tenosynovial Giant Cell Tumor - NORD (National Organization for Rare Disorders). [online] NORD (National Organization for Rare Disorders). Available at: <https://rarediseases.org/rare-diseases/tenosynovial-giant-cell-tumor>. Accessed 30 Sep. 2019.
6. Cassier PA, Gelderblom H, Stacchiotti S, et al. Efficacy of imatinib mesylate for the treatment of locally advanced and/or metastatic tenosynovial giant cell tumor/pigmented villonodular synovitis. *Cancer*. 2012;118(6):1649-55. doi: 10.1002/cncr.26409.
7. UpToDate, Inc. Treatment for tenosynovial giant cell tumor and other benign neoplasms affecting soft tissue and bone. UpToDate [database online]. Waltham, MA. Updated March 7, 2025. Available at: <http://www.uptodate.com/home/index.html>. Accessed June 10, 2025.
8. National Comprehensive Cancer Network. Soft Tissue Sarcoma. NCCN. January 2025. Accessed May 6, 2025. https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf

Related Policies

Currently there are no related policies.

Policy Implementation/Update

Action and Summary of Changes	Date
Addition of vimseltinib (Romvimza) to policy. Updated diagnostic criteria and renewal criteria to include biopsy and disease severity. Added criteria regarding prior treatment failure. Updated supporting evidence, E/I summary, and references.	08/2025
Updated to include 125mg tablet as the 200mg is discontinued; Updated renewal wording to include standard formatting; updated minor formatting things	01/2023
Turalio Policy created	09/2019

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Previous reviews	09/2019; 11/2019

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP148

Description

Pegvaliase (Palynziq) is a PEGylated phenylalanine-metabolizing enzyme that works to reduce blood phenylalanine concentrations by converting phenylalanine to ammonia and transcinnamic acid.

Sapropterin dihydrochloride (Kuvan) is a synthetic form of the cofactor BH₄ (tetrahydrobiopterin) for the enzyme phenylalanine hydroxylase (PAH). PAH hydroxylates phenylalanine to form tyrosine. BH₄ activates residual PAH enzyme, improving normal phenylalanine metabolism and decreasing phenylalanine levels.

Length of Authorization

- Initial:
 - Pegvaliase (Palynziq): Six months
 - Sapropterin dihydrochloride (Kuvan): Two months
- Renewal:
 - Pegvaliase (Palynziq): 12 months
 - Sapropterin dihydrochloride (Kuvan): 12 months

Quantity Limits

Product Name	Indication	Dosage Form	Quantity Limit
pegvaliase (Palynziq)	Phenylketonuria (PKU)	2.5 mg/0.5 mL	8 syringes/30 days
		10 mg/0.5 mL	30 syringes/30 days
		20 mg/1 mL	90 syringes/30 days
sapropterin dihydrochloride (generic Kuvan)		100 mg tablets	20 mg/kg/day
100 mg powder for oral solution			
500 mg powder for oral solution			
sapropterin dihydrochloride (Kuvan)		100 mg tablets	20 mg/kg/day
		100 mg powder for oral solution	
		500 mg powder for oral solution	
sapropterin dihydrochloride (Javygtor)		100 mg tablets	20 mg/kg/day
		100 mg powder for oral solution	
		500 mg powder for oral solution	

Initial Evaluation

- I. **Pegvaliase (Palynziq), sapropterin dihydrochloride (Kuvan), and sapropterin dihydrochloride (Javygtor)** may be considered medically necessary when the following criteria below are met:

- A. Medication is prescribed by, or in consultation with, a metabolic diseases specialist or a provider who specializes in the treatment of phenylketonuria and other metabolic disorders; **AND**
 - B. Documentation of current blood phenylalanine concentration is submitted; **AND**
 - C. Documentation noting member compliance with a phenylalanine restricted diet; **AND**
 - D. Member is going to continue to restrict phenylalanine from their diet; **AND**
 - E. A diagnosis of **phenylketonuria (PKU)** when the following are met:
 - 1. Request is for **generic sapropterin dihydrochloride**; **AND**
 - i. Member has uncontrolled blood phenylalanine concentrations greater than 360 micromol/L on existing management [e.g., phenylalanine restricted diet]; **AND**
 - ii. Not used in combination with pegvaliase (Palynziq); **OR**
 - 2. Request is for **pegvaliase (Palynziq)**; **AND**
 - i. Member is 18 years of age or older; **AND**
 - ii. Member has uncontrolled blood phenylalanine concentrations greater than 600 micromol/L on existing management [e.g., phenylalanine restricted diet, Kuvan (sapropterin)]; **AND**
 - iii. Not used in combination with sapropterin dihydrochloride (Kuvan); **OR**
 - 3. Request is for **dihydrochloride (Kuvan) or sapropterin dihydrochloride (Javygtor)**; **AND**
 - i. Member has tetrahydrobiopterin- (BH4-) responsive PKU; **AND**
 - ii. Member has uncontrolled blood phenylalanine concentrations greater than 360 micromol/L on existing management [e.g., phenylalanine restricted diet]; **AND**
 - iii. Treatment with generic sapropterin dihydrochloride (generic for Kuvan) has been ineffective, contraindicated, or not tolerated; **AND**
 - iv. Not used in combination with pegvaliase (Palynziq).
- II. Pegvaliase (Palynziq) and sapropterin dihydrochloride (Kuvan) is considered investigational when used for all other conditions, including but not limited to:
- A. Liver Cirrhosis and Portal Hypertension
 - B. Autism spectrum disorder
 - C. Gastroparesis
 - D. Schizophrenia

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. Attestation noting member compliance with a phenylalanine restricted diet; **AND**
- IV. Documentation of current blood phenylalanine concentration is submitted; **AND**

- V. Attestation of member compliance to therapy with pegvaliase (Palynziq) or sapropterin dihydrochloride (Kuvan; Javygtor); **AND**
- VI. Member had a response to pegvaliase (Palynziq) therapy defined as:
 - A. At least a 20% reduction in blood phenylalanine levels from baseline; **OR**
 - B. Blood phenylalanine concentration less than or equal to 600 micromol/L; **OR**
- VII. Member had a response to generic sapropterin dihydrochloride or sapropterin dihydrochloride (Kuvan; Javygtor) therapy defined as:
 - A. At least a 30% reduction in in blood phenylalanine levels from baseline; **OR**
 - B. Clinical response (e.g., cognitive and/or behavioral improvements)

Supporting Evidence

- I. Phenylketonuria (PKU) is an inherited disorder that increases the levels of a substance called phenylalanine in the blood. If PKU is not treated, phenylalanine can build up to harmful levels in the body causing intellectual disability and other serious health problems. Seizures, delayed development, behavioral problems, and psychiatric disorders are also common. Considering all the aspects of this disease state and that it is crucial to identify if a member is responding to therapy, the medication needs to be prescribed by, or in consultation with, a metabolic diseases specialist or a provider who specializes in the treatment of phenylketonuria and other metabolic disorders.
- II. It is crucial for treatment and prevention of disease progression to obtain the blood levels of phenylalanine (PHE) prior to treatment start.
- III. According to the American College of Medical Genetics and Genomics (ACMG) Practice Guidelines, dietary therapy, with restriction of dietary phenylalanine intake, remains the mainstay of therapy for PAH deficiency. The goal of the diet is to provide enough natural protein for the patient to be healthy and grow normally with sufficient restriction to keep blood phenylalanine in the treatment range. PKU medication is not a replacement for diet.
- IV. Pegvaliase (Palynziq) is FDA approved to reduce blood phenylalanine concentrations in adult patients with PKU who have uncontrolled blood phenylalanine concentrations greater than 600 micromol/L on existing management [e.g., phenylalanine restricted diet, Kuvan (sapropterin)].
- V. The safety and efficacy of pegvaliase (Palynziq) in pediatric patients has not been assessed in clinical trials and therefore there is no robust evidence to support the use. However, pegvaliase (Palynziq) has been approved in the European Union for patients aged 16 years or older with a dose regimen that mirrors adult dosing. Additionally, three open label phase 2 studies evaluating use of Palynziq in patients aged 16 years or older have been completed in the U.S. (NCT01560286, NCT00925054, NCT00924703) which show some signals of efficacy. However, studies have a small sample size, low enrollment of patients less than 18 years old, and possible safety concerns, thus true safety and efficacy of Palynziq in the subset of patients aged 16 to 18 years remains unknown.
- VI. There is no robust clinical trial data to show an increase benefit and the safety profile of concomitant use of pegvaliase (Palynziq) and sapropterin dihydrochloride (Kuvan).
- VII. ACMG guidelines note that approximately 25–50% of the patients with PAH deficiency are sapropterin-responsive. Patients with mild PAH deficiency are most likely to respond because some stable protein is required for sapropterin to function; nonetheless, responsive patients are

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identified even among those with complete PAH deficiency. Genotype may be predictive of sapropterin response, but genotype-phenotype correlations thus far are imperfect. Therefore, every PAH-deficient patient should be offered a trial of sapropterin therapy to assess responsiveness. Clinical judgment is required to determine what constitutes a significant or beneficial decline in an individual patient, but 30% is often cited in the literature as evidence of effective PHE reduction. Most sapropterin responsive patients have a rapid decline in blood PHE level, but occasionally a delay of 2–4 weeks is seen. Patients with a baseline PHE level at the lower end of the treatment range (180 $\mu\text{mol/l}$ or lower) rarely show a significant decline in blood PHE level, even if they are sapropterin-responsive. An improvement in neuropsychiatric symptoms or increase in PHE tolerance without a decrease in blood PHE in any patient constitutes sufficient justification to continue therapy. The blood phenylalanine concentration associated with optimal neurodevelopmental outcome is uncertain.

- VIII. For sapropterin dihydrochloride (Kuvan) the response to therapy is determined by change in blood phenylalanine following treatment. If blood phenylalanine does not decrease from baseline at 10 mg/kg per day, the dose may be increased to 20 mg/kg per day. Patients whose blood phenylalanine does not decrease after 1 month of treatment at 20 mg/kg per day are non-responders and treatment should be discontinued. However, an improvement in neuropsychiatric symptoms constitutes sufficient justification to continue therapy.
- IX. For pegvaliase (Palynziq) the response to therapy is determined by change in blood phenylalanine following treatment. In patients who have not achieved a response (at least a 20% reduction in blood phenylalanine concentration from pre-treatment baseline or a blood phenylalanine concentration less than or equal to 600 micromol/L) after 16 weeks of continuous treatment with the dosage of 40 mg once daily, can consider increasing to a maximum dose of 60 mg once daily. As recommended in the package insert, pegvaliase (Palynziq) should be discontinued in patients who have not achieved an adequate response after 16 weeks of continuous treatment with the maximum dosage of 60 mg once daily.

Investigational or Not Medically Necessary Uses

- I. Pegvaliase (Palynziq);
 - A. There is limited or no published clinical trial data to support the use of pegvaliase (Palynziq) in conditions other than PKU.
- II. Sapropterin dihydrochloride (Kuvan);
 - A. Liver Cirrhosis and Portal Hypertension
 - i. A randomized, blinded, and placebo-controlled trial was conducted to assess the effects of sapropterin dihydrochloride (Kuvan) on hepatic and systemic hemodynamics in patients with liver cirrhosis and portal hypertension. The trial data showed that sapropterin dihydrochloride (Kuvan), did not reduce portal pressure in patients with cirrhosis.
 - B. Autism spectrum disorder (ASD)
 - i. A prospective 16-week open-label outpatient treatment trial of sapropterin dihydrochloride (Kuvan) for core and associated ASD symptoms in 2–6-year-old children with confirmed language and/or social delays extended the

- Understanding of the effect of BH₄ treatment on the cognitive and behavioral symptoms of individuals with ASD
- ii. The results of a double-blind placebo-controlled crossover study, designed to examine the tetrahydrobiopterin pathway genes in autism, indicated a possible effect of BH₄ treatment in children with autistic disorder, but the study does not have enough power and it wasn't designed to show efficacy and safety of the use of sapropterin dihydrochloride (Kuvan) in the treatment of autism spectrum disorder. There is no robust safety and efficacy data to support the use of sapropterin dihydrochloride (Kuvan) in patients with autism spectrum disorder.

C. Gastroparesis

- i. One small open label trial consisting of low-quality evidence. Further evaluation is needed to support the use of sapropterin dihydrochloride (Kuvan) in this setting.

D. Schizophrenia

- i. One small open label trial consisting of low-quality evidence is available with ongoing trials recruiting as of 2019. Further evaluation is needed to support use of sapropterin dihydrochloride (Kuvan) in this setting.

16. ClinicalTrials.gov. A Study to Evaluate Subcutaneously Administered rAvPAL-PEG in Patients With Phenylketonuria for 24 Weeks. NCT01560286.
17. ClinicalTrials.gov. Dose-Finding Study to Evaluate the Safety, Efficacy, & Tolerability of Multiple Doses of rAvPAL-PEG in Subjects With PKU. NCT00925054.
18. ClinicalTrials.gov. Long-Term Extension of Previous rAvPAL-PEG Protocols in Subjects With PKU (PAL-003). NCT00924703.

Related Policies

Currently there are no related policies.

Policy Implementation/Update:

Action and Summary of Changes	Date
For sapropterin: Removal of BH4 responsiveness at initial as this is evaluated via medication trial. Updated renewal criteria to allow continuation in those with neurocognitive improvement as per ACMG guidelines. Removed requirement of specialist prescribing upon renewal, this update is applicable to all agents.	03/2023
Added branded sapropterin dihydrochloride (Javygtor) to policy	11/2022
Addition of generic sapropterin dihydrochloride (generic Kuvan) into policy, requiring trial of generic prior to brand. Updates to QL, allowing for 60 mg max dose. Formatting updates and updates to supporting evidence.	10/2021
- Updated criteria to policy format and combined separate policies into one - Ensured sapropterin dihydrochloride (Kuvan) is not used in combination with pegvaliase (Palynziq) - Requirement of member requesting sapropterin dihydrochloride (Kuvan) to have tetrahydrobiopterin- (BH4-) responsive PKU - Added criteria to require documentation of current blood phenylalanine concentration and of current compliance with a phenylalanine restricted diet - Adjusted requirement of phenylalanine levels in use of sapropterin dihydrochloride (Kuvan) to be greater than 360 micromol/L for all ages - Updated renewal duration with Kuvan to 1 year to align with Palynziq	12/2019
pegvaliase (Palynziq) policy effective	08/2018
sapropterin dihydrochloride (Kuvan) policy effective	02/2009

Policy Type: PA/SP

Pharmacy Coverage Policy: UMP020

Description

Sildenafil (Revatio, Liqrev), and tadalafil (Adcirca, Cialis, Alyq, Tadliq) are phosphodiesterase type 5 (PDE5) inhibitors.

Length of Authorization

- Initial: Length of benefit
- Renewal: Not applicable

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
sildenafil (Revatio)	Raynaud's phenomena Pulmonary arterial hypertension	20 mg tablets	90 tablets/30 days
		10 mg/mL suspension	224 mL/30 days (2 bottles)
sildenafil (Liqrev)	Pulmonary arterial hypertension	10 mg/ml oral suspension	122 mL/20 days
tadalafil (Cialis)	Benign prostatic hyperplasia	2.5 mg tablets	30 tablets/30 days
		5 mg tablets	
	Pulmonary arterial hypertension	20 mg tablets	60 tablets/30 days
tadalafil (Adcirca)	Pulmonary arterial hypertension	20 mg tablets	60 tablets/30 days
tadalafil (Alyq)	Pulmonary arterial hypertension	20 mg tablets	60 tablets/30 days
tadalafil (Tadliq)	Pulmonary arterial hypertension	20 mg/5 mL suspension	300 mL/30 days (2 bottles)

Initial Evaluation

- I. Medication contained in this policy may be considered medically necessary when the following criteria below are met:
 - A. A diagnosis of one of the following:
 1. **Pulmonary arterial hypertension (PAH); AND**
 - i. The medication is prescribed by or in consultation with a specialist (e.g., pulmonologist, cardiologist); **AND**
 - ii. The patient is classified as having World Health Organization (WHO) Functional Class II-IV symptoms; **AND**
 - iii. The request is for generic sildenafil tablets or generic tadalafil tablets; **OR**

- a. The request is for Revatio tablets or Adcirca and both generic sildenafil and generic tadalafil are found to be ineffective, not tolerated, or contraindicated; **OR**
 - b. The request is for generic sildenafil oral suspension 10 mg/mL, and the member is unable to swallow oral tablets; **OR**
 - i. The request is for brand Revatio oral suspension 10 mg/mL; **AND**
 - 1. generic sildenafil oral suspension 10 mg/mL, Tadliq oral suspension 20 mg/5mL, and Liqrev oral suspension 10 mg/mL have all been ineffective, not tolerated, or contraindicated; **OR**
 - ii. The request is for Tadliq oral suspension 20 mg/5mL or Liqrev oral suspension 10 mg/mL; **AND**
 - 1. Generic sildenafil oral suspension 10 mg/mL has been ineffective, not tolerated, or contraindicated; **OR**
 - 2. **Benign prostatic hyperplasia (BPH); AND**
 - i. At least one alpha-1 blocker AND one 5-alpha-reductase inhibitor medication have been ineffective, not tolerated, or both are contraindicated
 - a. Examples of 5-alpha reductase inhibitors: dutasteride, finasteride
 - b. Examples of alpha-1 blockers: alfuzosin, doxazosin, silodosin, tamsulosin, terazosin; **AND**
 - ii. Generic tadalafil 2.5 or 5 mg tablets are requested (please note, no other medications addressed in this policy are covered for BPH); **OR**
 - 3. **Raynaud's disease/phenomena; AND**
 - i. Generic sildenafil 20mg has been prescribed at a maximum quantity of 90 tablets per 30-day supply (please note, no other medications in this policy are covered for Raynaud's); **AND**
 - ii. Treatment with a dihydropyridine calcium channel blocker (e.g., nifedipine, amlodipine, isradipine, felodipine) or diltiazem has been ineffective, not tolerated, or is contraindicated; **OR**
 - a. Generic sildenafil 20mg tablets will be used in combination with a calcium channel blocker or diltiazem as additional treatment.
- II. Medications listed in this policy are considered not medically necessary when criteria above are not met and/or when used for:
- A. Erectile dysfunction.
- III. Medications listed in this policy are considered investigational when used for all other conditions, including but not limited to:
- A. Traumatic brain injury
 - B. Hypertension, not of the pulmonary arterial type
 - C. Heart failure and/or other cardiovascular or central nervous system conditions, disorders, or diseases

- D. Oncologic conditions
- E. Encephalopathy
- F. Cirrhosis

Renewal Evaluation

- I. Renewal criteria - Not applicable, approval allowed for length of benefit.

Supporting Evidence

- I. Pulmonary arterial hypertension: Pulmonary hypertension (PH) specific therapy is directed at the PH itself rather than the underlying cause of PH. Patients with persistent PH with World Health Organization (WHO) functional class II, III, or IV despite treatment of the underlying cause of PH should be evaluated for PH specific therapy. Group I patients should be observed and treated for the contributing factors. As of 2019, preferential treatments for group II-III patients include tadalafil plus other agents, and group IV should be treated with IV agents or double or triple combination therapy regimen that may or may not include tadalafil or sildenafil. Therapy is individualized to the patient and there are several suitable agents outside of sildenafil or tadalafil.
- II. Benign prostatic hyperplasia (BPH): common treatment for BPH include alpha-1 adrenergic antagonists, 5-alpha-reductase inhibitors, anticholinergic agents, and phosphodiesterase-5 (PED-5) inhibitors. As of 2019, it was recommended that those with mild disease should be considered for an alpha-1 adrenergic antagonist. This is due to 5-alpha-reductase inhibitors requiring long-term treatment for efficacy (six to twelve months of treatment required prior to symptom improvement); however, it shall be noted that some patients will experience hypotension with alpha-1-adrenergic antagonists. Alternative options beyond these two classes include anticholinergic agents and PDE-5 inhibitors.
- III. Raynaud phenomenon (RP): An exaggerated vascular response to cold temperature or emotional stress. This is manifested clinically by sharply demarcated color changes of the skin. Attacks occur commonly in the hands but may also occur in the toes, and attacks may cause symptoms such as numbness, clumsiness of the hand, aches, pains, or a feeling of pins and needles. Initial management of RP includes avoidance of triggers and vasoconstricting medications (e.g., nasal decongestants, amphetamines, ephedra, stimulants, triptans, ergotamines), as well as smoking cessation.
- IV. Initial pharmacologic management of RP is recommended with calcium channel blockers of the dihydropyridine type. Amlodipine is preferred, but other such as nifedipine may be used. Other agents, such as PED-5 medications (e.g., sildenafil, tadalafil, vardenafil) may be considered with calcium channel blockers are contraindicated or not tolerated.

Investigational or Not Medically Necessary Uses

- I. Erectile dysfunction treatment is deemed medically necessary by the plan and is excluded from coverage.

- II. All of the aforementioned indications, conditions, diseases listed in the experimental/investigational section and treated with medications in this policy are being evaluated in clinical trials. Safety and efficacy have not yet been determined.

References

1. Oregon Insurance Division Bulletin INS 2014 – 1 Mental Health Parity
2. Diagnostic and Statistical Manual of Mental Disorder (DSM) Version IV-TR and V.
3. Bancroft J, Wu FC. Changes in erectile responsiveness during androgen replacement therapy. Arch Sex Behav. 1983;12(1):59-66.
4. UpToDate. Cunningham GR, Kadmon D. Medical treatment of benign prostatic hyperplasia. May 13, 2019. Available at: https://www.uptodate.com/contents/medical-treatment-of-benign-prostatic-hyperplasia?search=benign%20prostatic%20hyperplasia&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1. Accessed May 29, 2019.
5. UpToDate. Hopkins W, Rubin LJ. Treatment of pulmonary hypertension in adults. March 22, 2019. Available at: https://www.uptodate.com/contents/treatment-of-pulmonary-hypertension-in-adults?search=pulmonary%20hypertension&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2. Accessed May 29, 2019.
6. Barnes H, Brown Z, Burns A, Williams T. Phosphodiesterase 5 inhibitors for pulmonary hypertension. Cochrane Database Syst Rev. 2019;1:CD012621.
7. UpToDate. Wigley FM. Clinical manifestations and diagnosis of the Raynaud phenomenon. February 11, 2018. Available at: https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-the-raynaud-phenomenon?search=raynauds%20phenomena&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1. Accessed May 29, 2019.
8. UpToDate. Wigley FM. Treatment of Raynaud phenomenon: initial management. April 22, 2019. Available at: https://www.uptodate.com/contents/treatment-of-raynaud-phenomenon-initial-management?search=raynauds%20phenomena&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2. Accessed May 29, 2019.
9. Zidek W, Spiecker C, Knaup G, Steindl L, Breuer HW. Comparison of the efficacy and safety of nifedipine coat-core versus amlodipine in the treatment of patients with mild-to-moderate essential hypertension. Hypertension Study Group. Clin Ther. 1995;17(4):686-700.
10. Roustit M, Blaise S, Allanore Y, Carpentier PH, Caglayan E, Cracowski JL. Phosphodiesterase-5 inhibitors for the treatment of secondary Raynaud's phenomenon: systematic review and meta-analysis of randomised trials. Ann Rheum Dis. 2013;72(10):1696-9.

Policy Implementation/Update:

Action and Summary of Changes	Date
Added Liqrev suspension into policy with a step through generic sildenafil suspension. Updated requirements of brand Revatio suspension to require step through generic product as well as Tadelq and Liqrev.	06/2023
Added tadelq suspension into policy criteria with a step through generic sildenafil suspension	11/2022
Added new product tadalafil (Tadelq) 20 mg/5 ml oral suspension	09/2022
Creation of policy from prior authorization criteria. Opened up criteria to allow for generic sildenafil and tadalafil for BPH and PAH due to generic availability.	05/2019
Updated PAH questions to remove contraindication questions, assess function classification of staging and trial and failure of generic sildenafil. Aligned with commercial PAH criteria. Added clinical note of Raynaud phenomena.	03/2018
Previous reviews	06/2015
Policy created	04/2015